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Peanut allergy and allergic airways inflammation

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Asthma is a major risk cofactor for anaphylactic deaths in children with peanut allergy. Peanut allergy is generally thought to be a lifelong condition, but some children outgrow their coexistent asthma. It has recently been shown that children who have 'outgrown' their asthma symptoms may have ongoing eosinophilic airways inflammation. The need for regular inhaled corticosteroid treatment in peanut allergic children and adolescents who have outgrown their asthma is however unclear. The aims of our study were to look at fractional exhaled nitric oxide levels (FeNO), as a non-invasive marker of eosinophilic airways inflammation, in peanut allergic children and assess whether children with outgrown asthma had elevated levels. Children with peanut allergy were recruited at two pediatric allergy clinics in Belfast, UK. Exhaled nitric oxide levels (FeNO) were measured using the Niox Mino in all children. Of the 101 peanut allergic children who consented for enrolment in the study, 94 were successfully able to use the NIOX Mino. Age range was 4–15 yr (median 10 yr); 61% were boys. Thirty (32%) had never wheezed, 37 (39%) had current treated asthma, 20 (21%) had at least 1 wheezing episode within the last year but were not taking any regular asthma medication (wheeze no treatment), and 7 (7%) had outgrown asthma. All children with outgrown asthma had elevated levels of FeNO (> 35 ppb), and 75% of children defined as 'wheeze no treatment' had elevated FeNO levels (> 35 ppb). Outgrown asthma and children defined as 'wheeze no treatment' had higher levels of FeNO than those with no history of wheeze or current treated asthma ($p = 0.003$). In children with peanut allergy, we found that those who had outgrown asthma had elevated FeNO levels in keeping with ongoing eosinophilic airways inflammation.

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Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death (NIAID 2006) (1). Within the pediatric population, food and particularly peanut allergy has been found to be the commonest cause of anaphylactic reactions (2). Reviews of fatal and near-fatal anaphylactic reactions have identified asthma, and in particular, poorly controlled asthma, as an important cofactor in these reactions (3).

Asthma can present in early childhood, and up to 60–70% of children will become asymptomatic during their adolescent years and appear to have 'outgrown' their asthma (4). However, it has now been shown that ongoing airways inflammation and airway remodeling may persist in these 'asymptomatic' adolescents (5).

Fractional exhaled nitric oxide (FeNO) is a non-invasive marker of eosinophilic airways inflammation. FeNO has been found to correlate with airway eosinophilia, measured by induced sputum (6), bronchoalveolar lavage (7) and mucosal biopsy (8). Elevated FeNO levels have been found in poorly controlled asthmatics, but levels reduce with the use of inhaled corticosteroid (ICS) or leukotriene receptor antagonist

(LTRA) therapy (9, 10). It has been proposed that FeNO can be used as a surrogate marker of disease activity in the control of chronic asthma; however, recent studies have given variable results (11). Other applications for FeNO in asthma management have been proposed, and they include prediction of steroid effect, prediction and prevention of exacerbations, and tapering of steroids dose in symptom-free children; these applications need to be further explored (12–13).

The objectives of our study were to look at FeNO, as a non-invasive marker of eosinophilic airways inflammation, in peanut allergic children and assess whether children with outgrown asthma had elevated levels.

Methods

Subjects and protocol

This was a prospective cohort study of children (< 16 yr) attending two pediatric allergy outpatient clinics in Belfast (The Ulster Hospital) and Royal Belfast Hospital for Sick Children (RBHSC), UK from February to November 2007. Entry criteria included the following measures: age ≥4 yr, a clinical history of an immunoglobulin E (IgE)-mediated allergic reaction to peanuts and either positive SPT (≥3 mm above the negative control) or specific IgE (RAST grade 3 or above, or specific IgE titer ≥3.5 kU_A/L). Exclusion criteria included chronic lung disease, e.g. cystic fibrosis, bronchiectasis, primary ciliary dyskinesia.

The same investigator on both sites reviewed the clinical history. A doctor-administered questionnaire was completed, which included detailed questions about food allergies, asthma, eczema, and allergic rhinitis. An assessment of the severity of the initial allergic reaction was made using a scale previously published by Hourihane (14) (Table 1). This scoring system correlates the amount of peanut protein ingested with clinical symptoms reported and defines reactions as mild, moderate, or severe.

All children enrolled in the study had peanut allergy; however, with regard to asthma diagnosis, children were classified into one of the following categories:

Never wheezed – children in this group had no history of wheezing.

Asthma treated – children in this group had current active asthma (i.e. wheeze within the last 12 months) and were taking regular asthma preventer medication (ICS).

Wheeze no treatment – this group included children who were not taking any regular asthma medication, as they thought their asthma was not troublesome, but occasionally would wheeze with a viral upper respiratory tract infection and who had wheezed within the last 12 months.

Asthma outgrown – this group included children who previously had a history of asthma requiring regular preventer medication, however, over the last 2 yr did not require any medication and had no symptoms, i.e. they appeared to have outgrown their asthma.

Skin prick testing

Skin reactivity to peanut, hazelnut, walnut, Brazil nut, grass pollen, dog dander, cat dander and house dust mite (ALK-Abello, Horsholm, Denmark) was assessed by skin prick tests. The positive control was histamine dihydrochloride (10 mg/ml), and the negative control was 0.9% saline. A positive reaction was defined as a weal diameter ≥3 mm above the negative control.

Specific IgE measurement

Blood samples were analyzed for specific IgE using the Immulite 2000 analyzer. Values were expressed as kU_A/L.

Table 1. Severity scoring scale for allergic reactions

	> ¾ nut eaten/>100 mg peanut protein	¼–¾ nut eaten/3–99 mg peanut protein	Fragment swallowed/<3 mg peanut protein	Mucosal touch, None eaten	Inhalation/skin contact only
Localized urticaria/pruritus	1	2	3	4	6
Generalized urticaria	5	7	8	10	12
Abdominal pain/vomiting/angioedema	9	11	13	16	18
Laryngeal edema/mild wheezing	14	15	17	19	20
Collapse/severe respiratory symptoms	21	22	23	24	25

Mild reaction: 1–5.
Moderate reaction: 6–13.
Severe reaction: 14–25.

Total IgE levels

Blood samples were analyzed for total IgE levels using the ImmunoCAP system, and results expressed as kU_A/L.

Fractional exhaled nitric oxide

Fractional exhaled nitric oxide levels were performed before spirometry (15). Testing was postponed if there was a history of asthma exacerbation or viral upper respiratory tract infection within the previous 4 wk. FeNO levels were measured online, by single breath technique, according to the recommendations of the American Thoracic Society (ATS) using the Aerocrine Niox Mino machine (18). This hand held device follows all essential aspects of the ATS and European Respiratory Society (ERS) 2005 equipment recommendations for measurement of FeNO (16). The average of two attempts was recorded.

Spirometry

Pulmonary function testing was performed using a hand-held visual incentive spirometer (MicroLab 3500; Micro Medical Ltd., Kent, UK) in accordance with published guidelines. The best of three attempts was recorded.

Ethics and consent

Parental, and where appropriate child participant, written informed consent was obtained. Ethical approval for the study was received from the Office for Research Ethics Committee NI (06/NIR03/B7) and research governance approval from the Royal Group of Hospitals and the Ulster Hospital, UK.

Statistical analyses

Descriptive statistics were reported as means and standard deviation (s.d.) if normally distributed, and ANOVA test with Dunnetts post hoc testing used for comparison. If data was asymmetrically distributed, descriptive statistics were reported as median and interquartile range (IQR). For comparative analysis, skewed data was $\log_e$ transformed, and comparison made using ANOVA with Dunnetts post hoc analysis. Fisher's exact test was used for comparison of categorical data.

We used backwards stepwise regression modeling to determine independent factors simultaneously associated with the Log_e FeNO. Regression coefficients with 95% CI and p values are described for the final regression model. A p value of < 0.05 was considered statistically significant.

Results

Over a 10-month period (February–November 2007), 101 children with peanut allergy and their parents were approached for enrolment in the study. Seven (7%) children were subsequently unable to use the Niox Mino machine; thus, they were excluded from the study.

Table 2. Demographic and clinical data of children in each of four asthma groups

	Never wheezed (n = 30)	Asthma treated (n = 37)	Wheeze no treatment (n = 20)	Asthma outgrown (n = 7)	p Value
Age (years) mean [IQR]	9.96 [7.6–12.8]	10.6 [8.3–13.1]	10.6 [8.1–13.8]	10.3 [7.97–11.3]	0.83
Male/Female	22/8	22/15	10/10	3/4	
Ever eczema number (%)	23 (77)	30 (81)	16 (80)	5 (71)	0.79
Allergic rhinitis number (%)	17 (57)	30 (81)	12 (60)	4 (57)	0.034
Severity of 1st reaction number (%)					0.58
Mild	1 (3)	2 (1)	0 (0)	0 (0)	
Moderate	19 (63)	20 (54)	9 (45)	2 (29)	
Severe	7 (23)	10 (27)	6 (30)	4 (57)	
Other nut sensitization number (%)					0.43
None	13 (43)	13 (35)	7 (35)	2 (29)	
1	6 (20)	11(30)	2 (10)	2 (29)	
2	2 (7)	4 (11)	5 (25)	1 (14)	
3	1 (3)	3 (8)	0 (0)	1 (14)	
Aeroallergen sensitization number (%)					0.86
None	2 (7)	1 (35)	2 (35)	0 (29)	
1	6 (20)	8 (22)	2 (10)	1 (29)	
2	6 (20)	5 (14)	4 (25)	1 (14)	
≥3	5 (17)	10 (27)	7 (0)	2 (14)	
Total IgE (kU_A/L) median [IQR]	162 [63–382]	642 [335–1744]	839 [347–959]	1098 [293–1953]	0.001

Of the 94 children (mean age: 10.3 yr, s.d. 2.8, range 4.9–15.2) successfully able to use the Niox Mino on at least one attempt, 67 (71%) were enrolled at the RBHSC, and 27 (29%) at the Ulster Hospital. There were 57 boys (61%); 37 girls (37%).

Table 2 reports demographic and clinical data on children enrolled in the study within each of the four asthma groups.

There was a significant difference between the numbers of children with reported allergic rhinitis in each of the four asthma groups (Fisher's exact test, $p = 0.034$). The histogram shown (Fig. 1) identifies that children with current treated asthma were more likely to have associated allergic rhinitis. There was no difference in the numbers of children with eczema in each of the four asthma groups (Fisher's exact test, $p = 0.79$). There was no significant difference in FeNO levels between children with or without allergic rhinitis ($p = 0.658$) or between those who had ever had eczema and those never suffering from eczema ($p = 0.362$).

The level of total IgE was significantly lower in children who had never wheezed compared to those who had a history of wheeze ever ($p = 0.001$). A positive correlation ($R = 0.48$, $p < 0.001$) was found between $\log_e$ total IgE levels and $\log_e$ FeNO levels (Fig. 2).

Spirometry results including FEV_1 ($p = 0.9$), FVC ($p = 0.3$) and MMEF ($p = 0.3$) did not differ significantly between the four asthma groups. FeNO levels were significantly higher in the children with asthma outgrown and wheeze no treatment groups, compared to those in the asthma-treated and never wheezed groups (Table 3 and Fig. 3).

Backward regression analysis was performed with the following variables entered: gender, asthma group, allergic rhinitis, eczema, height, ICS, LTRA, $\log_e$ total IgE, and house dust mite sensitization; all potential confounders of FeNO identified from the literature. Non-significant (significance level = 0.1) variables were removed from the model; asthma group, height, and total IgE were subsequently identified as significant contributors. Table 4 gives results of final regression analysis. In this study group, asthma group and $\log_e$ total IgE were found to be significant predictors of $\log_e$ FeNO ($p < 0.001$, R square = 0.36).

Discussion

In this study, we have found that children who have reportedly 'outgrown' their asthma, but not their peanut allergy, have high levels of exhaled nitric oxide suggesting ongoing eosinophilic airways inflammation. Similarly, peanut allergic

Fig. 1. Number of children with allergic rhinitis in each of four asthma groups.

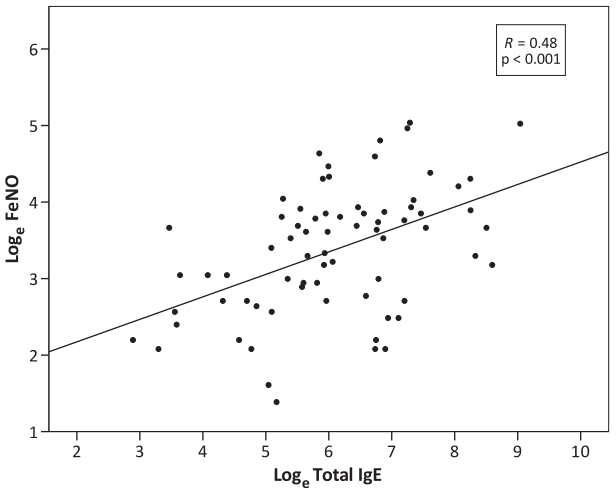

Fig. 2. Scatter plot of $\log_e$ total IgE against $\log_e$ FeNO (ppb).

Table 3. Spirometry and FeNO results for each of the four asthma groups

	Never wheezed (n = 30)	Asthma treated (n = 37)	Wheeze no treatment (n = 20)	Asthma outgrown (n = 7)	p Value
FEV_1 (% predicted) mean [IQR]	104 [98–114]	102 [96–109]	102 [88–115]	100 [93–109]	0.9
FVC (% predicted) mean [IQR]	98 [91–104]	103 [95–110]	101 [92–107]	95 [90–101]	0.3
MMEF (% predicted) mean [IQR]	102 [82–122]	89 [69–113]	93 [69–112]	94 [85–108]	0.3
FeNO (ppb) median [IQR]	21 [13–45]	28 [13–49]	48 [35–99]	51 [44–57]	0.003

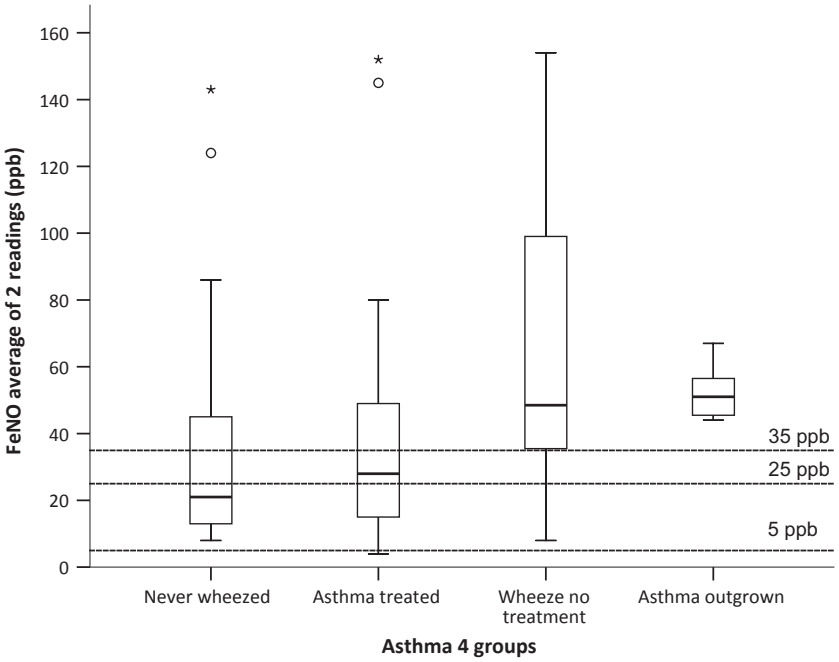

Fig. 3. Boxplot of asthma groups against average FeNO (ppb) (FeNO levels (23): < 5ppb, low; 5–25ppb, normal range for children; 25–35ppb, intermediate level; > 35ppb, high level. The central box extends from the 25–75th quartile with the median being marked by an internal line across the box. The whiskers extend 1.5 times IQR on either side or as far as the furthest observation within that range. Outliers (O) extend more than three times the IQR, with extreme outliers (*) being further than three times IQR from the end of the box.).

children who had occasional episodes of wheeze within the last year, but were not taking any regular ICS therapy (as their 'asthma' was not troublesome), had higher levels of FeNO compared to peanut allergic children who had either current active asthma and were taking regular asthma medication or those who had never wheezed. In addition, we have found that peanut allergic children who had current treated asthma were most likely to have concurrent allergic rhinitis compared to others in this study group. Children with peanut allergy who have never wheezed had the lowest level of total IgE. There was a significant positive correlation between $\log_e$ total IgE and $\log_e$ FeNO levels. In regression analysis, $\log_e$ total IgE and asthma group were significant contributors to $\log_e$ FeNO levels in this group of patients.

In 1992 Sampson reported 13 cases of fatal and near-fatal anaphylactic reactions to food in children and adolescents (17). This was the first study to recognize asthma as a significant cofactor in such reactions. Subsequently, Bock and Pumphrey have both reported on fatal food reactions and reinforced the finding of increased mortality in adolescents with coexistent peanut allergy and asthma (3, 18). Furthermore, it has been suggested that some asthmatic deaths may actually have been attributed to anaphylaxis and not asthma (19), and food allergy has been found to be an independent risk factor for potentially fatal childhood asthma (20).

Table 4. Final regression model (overall R = 0.601, p < 0.001), beta coefficients with 95% confidence intervals and p-values

Variable	Beta coefficient	95% CI	p-Value
Height	0.24	0.00–0.023	0.06
Asthma group	0.31	0.04–0.4	0.02
Log_e total IgE	0.33	0.04–0.4	0.02

In our study, all peanut allergic children with outgrown asthma had levels of FeNO above 35 ppb (actual range 44–67 ppb); a previously reported 'high' level of FeNO in children (21). Warke et al. identified elevated numbers of eosinophils in bronchoalveolar lavage fluid in children with 'outgrown' asthma (22). Obase et al. (4) found increased bronchial hyperresponsiveness (BHR) in asymptomatic adolescents with a history of asthma, and in agreement with our study, Den Toorn et al. identified elevated levels of FeNO (23). Thus, the term 'outgrown' asthma may in fact be misleading, and indeed many adolescents may be in clinical remission of their asthma symptoms but have ongoing subclinical airways inflammation. In adulthood, relapse of symptoms may occur, and in the longitudinal birth cohort in Dunedin (New Zealand), of the 164 adults currently wheezing at 26 yr, 46% had had a transient period of remission during their adolescent years (24). The current clinical significance of elevated FeNO in adolescents with outgrown asthma is debated. Den Toorn et al. have shown that treatment of adolescents in clinical remission of atopic asthma with ICS and LTRA therapy can result in a reduction in airway hyper-responsiveness and FeNO, with a suggestion that this may

influence airway remodeling in later life (25). Our study however comprises children/adolescents who not only have 'asthma remission' but who also have peanut allergy. Allergic reactions involving food allergens are more likely to involve the respiratory system compared to those following venom or iatrogenic-induced reactions, where shock has been found to be more commonly seen (26). A documented improvement in airway inflammation, as measured by FeNO, and a reduction in BHR following treatment with ICS or LTRA could be beneficial in the event of a future allergic reaction to peanuts in these individuals with 'remission' of their symptoms.

Children with occasional wheeze in association with a cold, 'wheeze no treatment' group in this study, had significantly higher levels of FeNO compared to children with current treated asthma or those with no history of wheeze. It is possible that these children/adolescents did not recognize ongoing symptoms of asthma and indeed had current untreated asthma hence the high levels. Pijnenburg and De Jongste proposed an algorithm for the interpretation of FeNO levels in asthmatic children (21). If we use this algorithm and consider this group as 'ICS naive asthmatics,' then 75% of our children have a high level of FeNO (>35 ppb), and a 'positive response to ICS therapy is likely'. Given their concurrent history of peanut allergy, an argument could thus be made for treating these children with ICS therapy to reduce airway inflammation and BHR and thus the theoretical risk of a severe allergic reaction.

Increased levels of FeNO have been found in patients with seasonal allergic rhinitis (AR) compared to non-atopic controls (27), and these levels have been found to increase during the pollen season (28). In our study, the presence of allergic rhinitis was assessed by the use of the ISAAC questionnaire. We found that children with current asthma were most likely to have allergic rhinitis, but this group did not have the highest levels of FeNO. Six children with allergic rhinitis were treated with nasal steroids, and 16 (25%) reported taking antihistamines for their symptoms. We also found that there was no significant difference in FeNO levels between children with or without allergic rhinitis. Aeroallergen sensitization has also been associated with elevated FeNO levels, particularly house dust mite. In this study, there was no significant difference in the numbers of children with aeroallergen sensitization between each of the four asthma groups, including house dust mite, nor was there a significant difference in FeNO levels between those sensitized to House Dust Mite (HDM) or not (data not shown). In the regression analysis, neither house dust mite sensitization nor allergic rhinitis was included in the final model, as they were not significant contributors to the FeNO levels. Thus, we feel that the elevated levels of FeNO identified in this study cannot solely be accounted for by the coexistence of allergic rhinitis or aeroallergen and particularly HDM sensitization.

Total IgE has previously been found to correlate with FeNO levels, and our study supports this finding (29). Furthermore, in regression analysis, total IgE was a significant contributor to FeNO levels. Total IgE has previously been shown to be an independent marker for asthma, and in this study total IgE was significantly higher in those children with any history of wheeze: current treated asthma, wheeze no treatment and outgrown asthma, compared to those who had never wheezed (30).

The primary aim of our study was to look at children with current peanut allergy and identify whether a subgroup of these children, i.e. those with outgrown asthma or who reported wheeze only in association with a cold, but were taking no regular treatment, had elevated levels of FeNO, suggesting underlying eosinophilic airways inflammation. Although the numbers of children in this study with outgrown asthma were small, the finding of significantly increased FeNO is potentially very significant in both research and clinical terms. Further studies, including an intervention arm such as prescription of ICS and further detailed lung function tests, including bronchial hyper-reactivity testing, to assess response are required to clarify some aspects of their significance.

The therapeutic implication, if any, of elevated FeNO levels in asymptomatic children is uncertain, and there is no agreed threshold level above which ICS treatment should be commenced. In this study, we have identified a group of children with peanut allergy who have no current clinical evidence of asthma but do have elevated FeNO and a history of wheeze. A limitation of our study is that we did not measure bronchial hyperreactivity which would have given additional information.

Teenage years are a time when asthma symptoms are typically outgrown, but this is also a risky period for severe allergic reactions to peanuts. While it is known that children with poorly controlled asthma are at greater risk of fatal anaphylaxis, it is not known whether this increased risk extends to those who have apparently outgrown their asthma. We have shown that such children have ongoing airways allergic

inflammation, and it seems intuitive that ICS should be used to damp down this persisting inflammation. However, because of the rarity of fatal anaphylaxis events, it will be difficult to prove whether such a strategy will be beneficial in the long term for reducing fatal or very severe episodes.

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