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ORIGINAL ARTICLE **Asthma and Rhinitis**

The complexities of defining atopy in severe childhood asthma

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Summary

Background Defining atopy in children with severe, therapy-resistant asthma is complex. There is currently no gold standard test; both skin prick testing (SPT) and allergen-specific IgE (sIgE) are used. Furthermore, atopy is increasingly considered to be a spectrum, not an all-or-none phenomenon.

Hypothesis SPTs and sIgE cannot be used interchangeably, and if both tests are not performed, opportunities for intervention will be missed. Furthermore, the severity of atopy will be defined differently by the two tests.

Methods Cross-sectional study of 47 children with severe, therapy-resistant asthma, mean age 11.8 years, range 5.3–16.6 years, who underwent SPT, and measurement of total and sIgE as part of their clinical work-up.

Results Overall, 42/47 (89%) were atopic (defined as either one positive SPT or sIgE). There was 98% concordance between the two tests in classifying atopy. When each allergen was considered individually, in 40/200 (20%), the SPT and sIgE results were discordant, most commonly in 25/200 (12.5%), the SPT was negative and the sIgE was positive. House dust mite and cat sensitization were more likely detected by sIgE, but dog sensitization by SPT. When atopy was quantified, the sum of sIgEs compared with the sum of SPT weal diameter showed a moderate correlation ($r^2 = 0.44$, $P < 0.001$). Total IgE increased with an increasing number of positive sIgEs ($P = 0.028$), but not significantly with increasing numbers of positive SPTs.

Conclusion and Clinical Relevance SPT and sIgE identify group prevalence of atopy equally well; however, for individual allergens, concordance is poor, and when used to quantify atopy, SPTs and sIgE were only moderately correlated. In a clinical setting, if allergen avoidance is contemplated in children with severe, therapy-resistant asthma, both tests should be performed in order to detect sensitization.

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Introduction

Severe, therapy-resistant asthma is a label applied to children referred for the assessment of asthma manifest by any of chronic symptoms, acute severe exacerbations and fixed airflow obstruction apparently unresponsive to high-dose medication [1]. These children have undergone intensive investigation to exclude a wrong diagnosis, asthma with important co-morbidities and difficult asthma (in which potentially modifiable factors have not been identified and remedied). As part of the assessment of these children, a nurse-led home visit is undertaken. Close attention is paid to environmental tobacco smoke exposure, psychosocial issues, adherence to treatment and environmental allergen exposure [2]. As a result of this strategy, less than 50% of children undergo further investigations and are considered to have severe, therapy-resistant asthma.

Ongoing exposure to allergens to which the child is sensitized is associated with a risk of exacerbations of asthma [3], and also causes steroid resistance by IL-2- and IL-4-mediated mechanisms [4, 5]. Thus, reduction of allergen burden in sensitized children with severe, therapy-resistant asthma is a logical strategy. Sensitization can be measured by skin prick tests (SPTs) or allergen-specific IgE (sIgE). In adults with severe asthma with fungal sensitization, and children with less severe asthma, the concordance between the two is 76–83% [6–8] but there are no data on

children with really severe asthma. SPTs tend to be conducted first because they are cheaper and the results are readily available, with sIgE used if there is a contraindication to SPT (such as severe eczema, known risk of anaphylaxis, when antihistamines cannot be stopped) or at a later date for further allergic assessment. It has been proposed that these tests be used in a complementary fashion, with SPT as a screening test as it is more sensitive and sIgE for confirmation as it is more specific [9–11].

We hypothesized that SPTs and sIgE cannot be used interchangeably, and that if both tests are not performed, opportunities for intervention in children with severe, therapy-resistant asthma will be missed.

Methods

Patients

Approval was granted by the ethics committee at the Royal Brompton Hospital, informed consent from the parents and age-appropriate assent to testing from the children. Children aged 6–16 years being assessed for severe therapy-resistant asthma between September 2004 and June 2009 followed a defined protocol. Entry criteria were a diagnosis of asthma with persistent symptoms ($\geqslant$3 days/week) or frequent exacerbations ($\geqslant$one a month) despite high-dose corticosteroids (budesonide $\geqslant$800 μg/day or fluticasone $\geqslant$500 μg/day), long-acting β_2-agonist (salmeterol $\geqslant$50 μg/day or eformeterol $\geqslant$12 μg/day) and montelukast (5–10 mg/day) or a previous failed trial of these treatments.

Subjects underwent a thorough assessment of their asthma as part of the protocol, including SPT [2]. If asthma was still poorly controlled after initial management was optimized, they went on to have further assessment, including sIgE and total IgE measurement (Fig. 1) [12].

Skin prick testing

Each subject underwent SPTs to a standard panel of five aeroallergens: house dust mite (HDM), cat, dog (canis familiaris), grasses (Avena Dactylic, Poa, Festuca, Lolium and Phleum) and trees (Alnus, Betula and Corylus). Additional allergens were added at the clinician's discretion and included fungi: aspergillus, alternaria, cladosporium; foods: peanut, milk, egg, shrimp, almond; animal derivatives: horse hair, hamster, poultry feathers, guinea-pig; and others: cockroach, latex or birch.

SPTs were performed by experienced respiratory nurses using standardized extracts (ALK-Abello, Hørsholm, Denmark) and positive and negative controls.

A result was deemed to be positive if the weal diameter was $\geqslant$3 mm. Subjects were classified as 'atopic on SPT' if one or more SPT was positive.

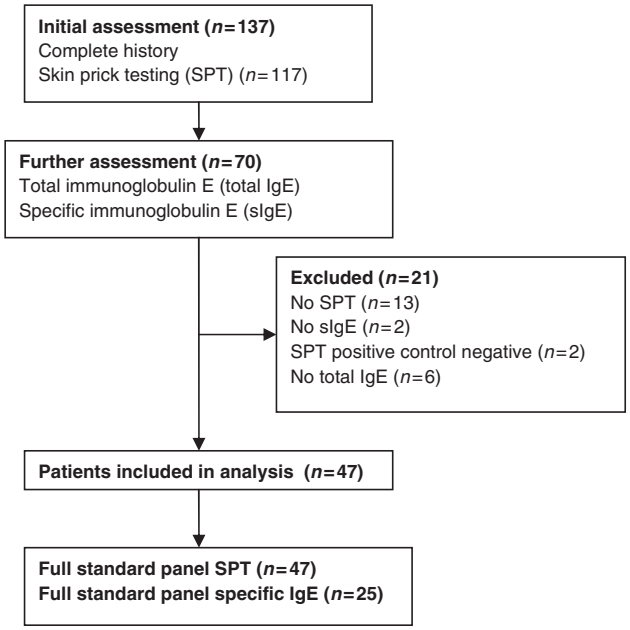

Fig. 1. Flow diagram of patients. SPT, skin prick test.

Allergen-specific immunoglobulin E antibodies

sIgE assays were performed in the Royal Brompton Hospital Laboratory using the ImmunoCAP 250 analyser (Phadiatop, Pharmacia, Uppsala, Sweden). A result was deemed positive if sIgE was $\geqslant$0.35 IU/mL. The standard panel consisted of HDM, cat, dog (dog dander), mixed grasses (*Anthoxanthum odoratum*, *Lolium perenne*, *Phleum pratense*, *Secale cereale* and *Holcus lanatus*) and mixed trees (*Acer negundo*, *Betula verrucosa*, *Corylus avellana*, *Quercus alba* and *Platanus acerifolia*). Additional allergens were tested at the clinician's discretion including those listed above for SPTs and foods: cheese, soy; animal derivatives: mouse; and others: hazelnut and weed pollens (*Artemisia vulgaris*, *Plantago lanceolata*, *Chenopodium album*, *Solidago virgaurea* and *Urtica dioica*). Subjects were classified as 'atopic on sIgE' if one or more sIgE was positive.

Total immunoglobulin E

The total IgE levels were measured from the same blood sample as sIgE using the Beckman Access immunoassay (Beckman Coulter Ltd, High Wycombe, UK), measured in IU/mL.

Statistical analysis

Analysis was performed and figures were generated using GraphPad Prism version 5.02. Non-parametric tests were used as data were not normally distributed. Categorical data were analysed using Fisher's exact or χ^2-tests as

Table 1. Patient demographics

Characteristic	Result ($n = 47$)	Result ($n = 25$)
Age, years, mean±SD (range)	11.8±2.7 (5.3–16.6)	12.2±2.9 (7.2–16.6)
Gender, male : female	23 : 24	9 : 16
Age at onset of asthma symptoms, months, median (range)	17 (0–144)	16 (0–144)
Previous intubation, *N*/*n* available (%)	8/47 (17)	6/25 (24)
Number of admissions in the last year, median (range)	2 (0–20)	2 (0–12)
% predicted FEV_1/FVC post-bronchodilator, median (range)	87.9 (45.5–101.2)	88.4 (53.4–101.1)
Total serum IgE, IU/mL, median (range)	318 (7–4610)	415 (8–1863)
Atopic on SPT, ⩾1 positive SPT, *N*/*n* available (%)	41/47 (87)	16/25 (64)
Atopic on sIgE, ⩾1 positive specific IgE, *N*/*n* available (%)	42/47 (89)	19/25 (76)

FEV_1, forced expiratory volume in 1 s; SPT, skin prick test.

appropriate, and numerical data were analysed using the Mann–Whitney two-sided test. Kruskal–Wallis one-way ANOVA was used if more than two groups were compared. The Spearman test was used for correlation, with results expressed as r^2. Total IgE data were log transformed for graphical purposes but all statistical analyses were performed on raw data.

Results

Demographics

Table 1 summarizes the baseline demographics. The mean age was 11.8±2.7 (range 5.3–16.6) and 23/47 (49%) were male. The median age of onset of symptoms was 17 months, 8/47 (17%) had a history of previous intubation, and the median number of hospital admissions in the past year was two admissions (range 0–20).

Comparison of skin prick test and allergen-specific immunoglobulin E antibodies

Overall, 42/47 (89%) subjects were classified as atopic. 41/47 (87%) were atopic on the basis of SPT and 42/47 (89%) were atopic on sIgE. One subject was not atopic on SPT but was atopic on sIgE. There was 98% concordance between the two tests in classifying children as atopic or non-atopic.

When each allergen of the standard panel was considered individually (Fig. 2), in 40/200 (20%), the SPT and sIgE result were discordant (Table 2). Twenty-five out of 200 (12.5%) of all paired SPT/sIgE for individual allergens had a negative SPT but a positive sIgE, and 15/200 (7.5%) had a positive SPT and a negative sIgE. Table 2 shows that, considering each allergen separately, sIgE was more frequently positive for most allergens (HDM, cat, trees and grasses), whereas dog sensitization was detected more frequently by SPT.

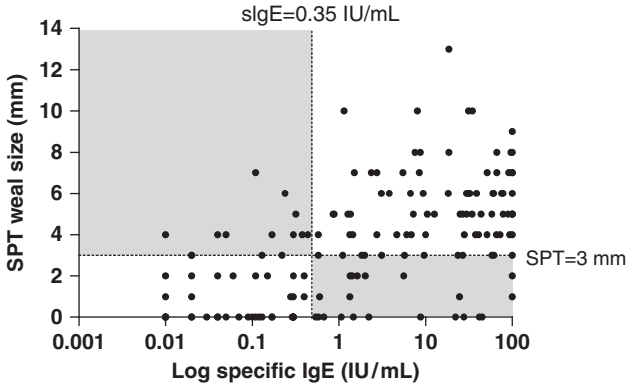

Fig. 2. Comparison of the specific IgE (sIgE) level and skin prick test (SPT) weal diameter for each individual allergen from the standard panel. Includes all allergens tested on each patient for which there are paired SPT and sIgE data ($n = 200$). Dotted lines at cut-offs for a positive test result – sIgE ⩾ 0.35 IU/mL, SPT ⩾ 3 mm. Discordant results are indicated by shaded areas.

When atopy was quantified, and the sum of sIgE (absolute values in IU/mL) from the standard panel was compared with the sum of SPT weal diameter from the standard panel, there was a moderate correlation ($r^2 = 0.44$, $P < 0.001$). There was a very good correlation between the total IgE and the sum of sIgEs ($r^2 = 0.83$, $P < 0.001$). The correlation between the total IgE and the sum of SPT weal diameter was poor ($r^2 = 0.28$, $P < 0.001$).

Serum total immunoglobulin E

Total IgE increased with an increasing number of positive sIgEs ($P = 0.028$) as can be seen in Fig. 3; however, when compared with increasing numbers of positive SPTs, this did not reach significance ($P = 0.084$).

Total IgE was significantly higher in those with at least one positive SPT (any SPT^+) compared with those with all negative SPTs (all SPT^-) ($P = 0.028$) and in those with at least one positive sIgE (any $sIgE^+$) compared with those with all negative sIgE (all $sIgE^-$) ($P = 0.018$) (Fig. 4).

There was no significant correlation between total IgE and age, total IgE and % predicted forced expiratory volume in 1 s/forced vital capacity post-bronchodilator, $r^2 = -0.004$ ($P = 0.68$, 95% CI = −0.37 to −0.26) or total IgE and number of hospital admissions for asthma over the previous year, $r^2 = 0.002$ ($P = 0.79$, 95% CI = −0.27 to 0.35).

Table 2. Comparison of each individual skin prick test (SPT)/specific IgE (sIgE) pair from the standard panel, showing the total number of discordant results

Allergen	$SPT^{-}sIgE^{+}$	$SPT^{+}sIgE^{-}$	Total number of discordant results
House dust mite ($n = 44$)	7	0	7
Cat ($n = 45$)	8	1	9
Dog ($n = 45$)	1	11	12
Grasses ($n = 41$)	5	2	7
Trees ($n = 25$)	4	1	5
Total ($n = 200$)	25/200 (12.5%)	15/200 (7.5%)	40/200 (20.0%)

n, number of paired SPT and sIgE results.

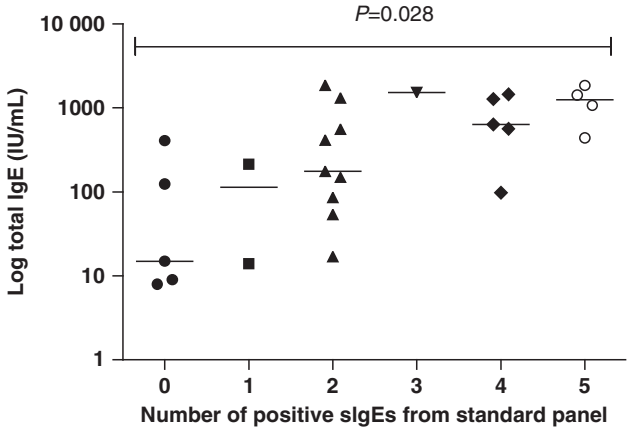

Fig. 3. Number of specific IgE antibodies (sIgEs) from the standard panel compared with total serum IgE.

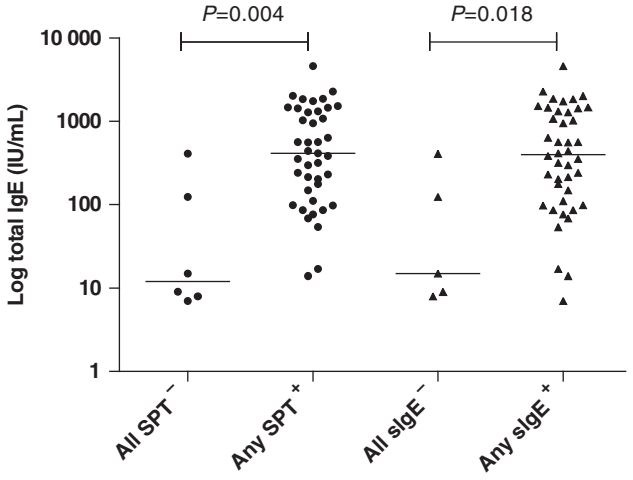

Fig. 4. Skin prick test (SPT) and specific IgEs (sIgEs) as positive or negative compared with total IgE.

Discussion

In this cross-sectional study of a cohort of children with severe, therapy-resistant asthma, we found that although SPT and sIgE identified the group prevalence of atopy equally well (with 98% concordance), for some specific allergens, concordance was poor. sIgE was more frequently positive than SPT for most common aero-allergens (HDM, cat, trees and grass), although for dog allergen, SPT was more often positive. The small numbers tested precluded comparison of other allergens. Total IgE correlated significantly with an increasing number of positive sIgEs but not with the number of positive SPTs, as might be expected. Finally, there is only a loose agreement between the severity of atopy as determined by the sum of sIgEs and the sum of SPT weal diameters.

This is the first study to address the complexities of defining atopy in children with severe asthma, a group in which the correct diagnosis of atopy and identification of sensitization to individual allergens is of particular importance. Exposure to allergens in a sensitized patient can cause poorly controlled asthma [13]. Ongoing allergen exposure is one of the most important modifiable factors, and appropriate interventions can potentially avoid escalation of medical therapy [2]. Furthermore, before treatment with the monoclonal anti-IgE antibody omalizumab is undertaken, it would seem logical to minimize environmental exposure to relevant allergens.

There are a number of limitations to the study. True severe asthma is an uncommon condition and so some of the analyses were on small numbers of children. Furthermore, 23 of 70 children had missing data and had to be excluded. We now have a more robust data collection procedure to minimize this problem. This study was carried out in a clearly defined population of children with severe asthma; hence, the results may not be applicable to children with mild to moderate asthma. We did not collect data on clinical allergy, as opposed to sensitization, but allergens may exert deleterious effects even without apparently causing symptoms [14]. We acknowledge that we have no outcome data as to whether allergen avoidance based on SPTs or sIgE was clinically beneficial. However, it has been shown that allergen sensitization and exposure are important risk factors in exacerbations in childhood asthma and that allergen load is susceptible to modification [3]. Accurately identifying allergen sensitization can help to identify key areas for intervention. We also note that there were some differences in the extracts tested between SPT and sIgE allergens from mixed trees, mixed grasses and dog. Differences between commercial

extracts have been recognized as a problem, especially with regard to breed-specific differences in dog allergy [15, 16]. This further emphasizes the need to perform both tests to identify as many allergens as possible.

Our results support those of a previous adult study focusing specifically on patients with severe asthma and fungal sensitization. We found 80% overall concordance for individual allergens. O'Driscoll et al. [6] found 77% concordance between the two tests and concluded that using both SPT and sIgE was necessary to identify all cases of fungal sensitization. However, our results contrast with previous evidence that SPTs provide more information on sensitivity to individual allergens [7]. Rather, we found that for most allergens, sIgE was more frequently positive, although for many, the numbers are small. This may be because serum IgE levels are thought to peak between 6 and 15 years of age, whereas sensitization measured by SPTs continues to increase into adulthood (25–27 years) [17], and our study population is aged 6–16 years. Thus, if the subjects had been followed longitudinally, more SPTs may have become positive, and our results may not be relevant to adult asthmatics.

Currently, the role of total IgE in asthma and atopy is controversial. The prevalence of asthma, independent of atopy, has been shown to be closely related to serum IgE, and may even be a direct consequence of asthma itself [18–20]. Furthermore, there is significant tracking of IgE with age [21]. A large study by Carroll et al. [22] in children with varying severity of asthma found strong associations between both total IgE and SPT weal diameter and markers of asthma severity. In our cohort with severe asthma, we did not find any correlation between total IgE, SPTs or number of hospital admissions in the past year. It is probable that at the severe end of the spectrum, total IgE adds little further information to predict severity. Recent evidence from a large birth cohort study by Simpson and colleagues suggested that IgE antibody responses do not equate to atopy, but rather are intermediate phenotypes of a true atopic vulnerability, each phenotype relating to differences in asthma severity [23, 24]. If this is the case, the frequently used definition of atopy (and the one we have used in this study) of a single positive SPT or sIgE is too arbitrary and that atopy is not an all-or-none phenomenon. We have demonstrated that using sIgE and SPTs in the assessment of atopy severity is only loosely correlated.

The results of this study have important clinical relevance. In children with severe therapy-resistant asthma, in whom the identification and removal of specific allergens is being contemplated, SPT and sIgE testing should be used in a complementary manner. Rather than performing SPT in the first instance in the management of children with severe therapy-resistant asthma, followed by further testing including sIgE at a later stage, both tests should be performed at the outset in order to more accurately identify sensitization to individual allergens.

Further work is needed to determine whether allergen avoidance is an effective strategy in severe therapy-resistant asthma, as has been suggested in more mild asthma [13, 25], and if so, how best to determine which allergens are important.

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