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Sensitivity and exposure to indoor allergens in adults with differing asthma severity

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ABSTRACT: In asthma, it is uncertain whether there is an association between degrees of exposure to domestic allergens and asthma severity. The pattern of sensitivity and exposure to common indoor allergens was examined in subjects with differing asthma severity.

Sensitivity to house dust mite, dog and cat allergen and exposure to *Der p* 1, *Can f* 1 and *Fel d* 1 were assessed by skin prick tests and settled dust analysis in 28 subjects with severe asthma and 28 age- and sex-matched subjects with mild asthma (two declined skin prick test).

All severe asthmatic subjects had at least one positive skin test and 20 of the 28 subjects were positive to all three allergens. Fourteen of the 26 subjects with mild asthma who took skin prick tests were positive to at least one, and one of these subjects was positive to the three allergens tested. Except for bedroom *Fel d* 1, the proportion of severe asthmatics both sensitized and exposed to each allergen at each site was significantly greater than the proportion sensitized and exposed in the mild asthma group. The geometric mean allergen concentrations, with the exception of bedroom *Fel d* 1, were greater in sensitized severe asthmatics than the sensitized mild asthmatics, which was significant for *Der p* 1 in bedroom samples and *Can f* 1 in bedroom and living room samples.

These results support an association between the degrees of domestic allergen exposure in sensitized individuals and asthma severity.

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While the majority of patients with asthma have mild disease, the medical, social and financial costs of asthma to society tend to be related to its severity. In the UK, the total financial costs (excluding asthma deaths) attributable to the most severe quintile of asthmatics account for around 60% of the total national expenditure on asthma [1].

The understanding of the pathogenesis of mild-to-moderate asthma has advanced considerably and the importance of exposure to house dust mite allergen in the expression of mild-to-moderate asthma is now well recognized. Between 45 and 85% of patients with asthma in the UK show skin test reactivity to mites [2]. Household exposure above threshold levels of *Der p* 1 in infancy is positively associated with the prevalence of skin test positivity and increased levels of specific immunoglobulin (Ig)E to mites [3] and an increased risk of asthma [4] in childhood. Studies in populations newly exposed to mites [5] and of populations living at altitude [6] also support the association between the presence of mite allergens and asthma. More recently, a relationship between levels of *Der p* 1 in the home and current symptoms in mild-to-moderate asthma has been suggested [7, 8], implying that mite allergen exposure may be important in the maintenance of ongoing disease activity in this group. In populations where mites are uncommon, sensitivity to other domestic allergens appears to be important in the development and maintenance of disease activity in mild-to-moderate asthma [9, 10]. Regardless of severity, the relationship between sensitivity and exposure to pet allergens, and indices of asthma morbidity remains poorly defined.

It remains unclear whether individuals with more severe disease are both sensitized and exposed to greater amounts of allergen than individuals with less severe disease, or if they have a lower threshold for exacerbation of symptoms, or both.

A subgroup within the population of severe asthmatics are those with "brittle asthma" (BA) [11]. A classification of BA into types 1 and 2 [12] has previously been proposed, type 1 being characterized by repeated life-threatening attacks of asthma with a background of wide peak expiratory flow (PEF) variability despite considerable medical therapy [13]. The factors responsible for the type 1 BA phenotype are speculative but an association with high atopy scores [14], high levels of psychosocial morbidity [15] and abnormal coping strategies for dealing with deteriorating asthma [16] has previously been demonstrated.

This study examines the sensitivity and exposure status of subjects with severe (SA) and mild (MA) asthma (defined on the basis of daily inhaled steroid dose) to mite, cat and dog allergen, using skin prick tests and settled dust analysis. The SA group comprises subjects with BA and nonbrittle SA (NBSA).

Methods

Subjects

Patients who fulfilled the diagnostic criteria for type 1 BA (>40% diurnal variation in PEF for >50% of days over a period of at least 150 days, despite considerable medical therapy, including a total daily dose of inhaled steroids of at least 1,500 mg of beclomethasone (BDP) or equivalent [13]), and who were willing to participate were identified from the West Midlands Brittle Asthma Register. Patients with SA but not BA (<25% diurnal variation in PEF for >50% of days over a period of at least 150 days) matched for age (within 5 yrs), sex and inhaled steroid dose (within 500 $\mu g \cdot day^{-1}$ BDP or equivalent) were identified from the asthma outpatient clinic at Heartlands Hospital. A further group of age- and sex-matched patients with MA (inhaled corticosteroid <800 $\mu g \cdot day^{-1}$ BDP or equivalent) were recruited at random from the same asthma clinic, two per index case. All subjects gave written informed consent and the study was approved by the East Birmingham Research & Ethics Committee. Demographic details including current asthma medication and the presence of pets in their homes were recorded.

Spirometry

Forced expiratory volume in one second (FEV_1) was measured in each subject with a Vitalograph (Buckinghamshire, UK) dry bellows spirometer. The best of three reproducible and technically acceptable blows was accepted. Results were expressed in terms of per cent of the predicted performance achieved [17].

Skin prick testing

Skin prick tests were performed using positive (histamine) and negative control solutions and *Dermatophagoides pteronyssinus* (house dust mite), cat and dog allergen solutions (Bencard, Welwyn, UK). Mean weal diameters (MWD) were read after 15 min. A positive response was defined as an MWD larger by 3 mm or more than the MWD of the negative control solution [18].

Dust sampling and allergen assays

Dust samples were collected from 1 m^2 targets, vacuumed for 2 min using a Medivac dust sampler (airflow of 45 $L \cdot s^{-1}$) (Medivac plc, Wilmslow, UK) onto a 5 mm vinyl filter (Plastok Associates Ltd, Wirral, UK). Samples were obtained from living room carpets, living room sofas, bedroom carpets, bedding and mattresses.

Fine dust (100 mg) was extracted from each sample by rotation for 2 h at room temperature with 2 mL of borate-buffered saline with 0.1% Tween-20®, pH 8.0, and then centrifuged for 20 min at 2,500 rpm at 4°C. Supernatants were stored at -20°C for future analysis. All samples were analysed blind for *Der p* 1 (house dust mite allergen), *Fel d* 1 (cat) and *Can f* 1 (dog). *Der p* 1 and *Fel d* 1 were assayed using two site monoclonal antibody (mAb)-based enzyme-linked immunosorbent assays (ELISA) as previously described [19, 20]. The standard used to establish the control curve for the *Der p* 1 assay (UVA 93/02) was considered to contain 2,500 ng *Der p* $1 \cdot mL^{-1}$. The UVA 91/01 standard for *Fel d* 1 contained 2 U *Fel d* $1 \cdot mL^{-1}$.

Can f 1 was measured by a two-site mAb ELISA using anti-*Can f* 1 mAb 6E9 for allergen capture and polyclonal rabbit anti-*Can f* 1 for detection [21]. Dust extracts were initially assayed at 5-, 25- and 125-fold dilution for carpets and bedding samples and at 100-, 500- and 2,500-fold dilutions for sofa samples. The assay was quantitated using doubling dilutions of dog allergen standard (UVA 94/02) from 500 $IU \cdot mL^{-1}$ to 1 $IU \cdot mL^{-1}$ *Can f* 1. The UVA 94/02 (10,000 $IU \cdot mL^{-1}$ *Can f* 1) was substandardized against World Health Organization (WHO)/IUIS International Reference Preparation of dog hair and dander (National Institute for Biological Standards and Control (NIBSC) 84/685). One International Unit is approximately 1 ng of *Can f* 1 protein, this value was used to calculate the results.

In samples where allergen concentrations were below the detection limit, for *Der p* 1 a value of 100 $ng \cdot g^{-1}$ of dust was assigned, for *Can f* 1 and *Fel d* 1 a value of 200 $ng \cdot g^{-1}$ of dust was assigned, corresponding to the lower limit of detection of the assays. All results are expressed as micrograms of allergen per gram of fine dust.

Definitions of "sensitivity" and "exposure"

"Sensitivity" to an allergen was defined as the presence of a positive skin prick to that allergen. "Significant exposure" to an allergen was defined as the presence of that allergen in settled dust sampled from any site at a concentration greater than or equal to a predetermined significant value. The values chosen for *Der p* 1, *Fel d* 1 and *Can f* 1 were 2 [22], 8 [23] and 10 $\mu g \cdot g^{-1}$ [9] of dust, respectively.

Statistical analysis

Analyses were performed with Epi Info V6.1 (USD Inc., USA) and Excel (Microsoft Corp., Redmond, WA, USA). Means of normally distributed data were compared by two-tailed Student's t-tests. Allergen concentrations followed a log-normal distribution and results are reported as geometric means with 95% confidence intervals (CI), and where between group comparisons were made two-tailed Student's t-tests were performed on natural log transformed data. Proportions were compared by Chi-squared and Fisher's exact tests where appropriate. Statistical significance was accepted at the 5% level.

Results

Subject demographics

Nineteen subjects with fully characterized type 1 BA and who were willing to participate in the study were identified. Fifteen age-, sex- and inhaled steroid dose-matched subjects with NBSA were willing to participate. Two age- and sex-matched subjects with MA were identified for 14 of these pairs, resulting in 56 (14×4) subjects for analysis, the SA group comprising those with BA and NBSA.

Table 1. – Geometric mean concentrations ($\mu g \cdot g^{-1}$) with 95% confidence intervals of allergen in settled dust by type, site and group

	Sofa	LR carpet	Mattress	Bedding	BR carpet
Der p 1					
Mild asthma	2.65 (1.32–5.35)	2.35 (1.13–4.91)	1.54 (0.68–3.49)	1.36 (0.69–2.66)	1.03 (0.51–2.07)
Severe asthma	1.97 (0.97–4.00)	1.27 (0.64–2.52)	3.45 (1.18–10.10)	6.91 (2.90–16.50)	3.80 (1.35–10.65)
Can f 1					
Mild asthma	1.95 (0.91–4.18)	2.71 (1.20–6.12)	0.77 (0.41–1.45)	0.88 (0.49–1.59)	1.16 (0.52–2.59)
Severe asthma	20.80 (8.36–51.72)	16.29 (6.32–42.01)	4.69 (1.72–12.83)	10.50 (4.17–26.47)	9.11 (3.18–26.07)
Fel d 1					
Mild asthma	3.52 (1.81–6.85)	5.69 (2.30–14.10)	0.98 (0.49–1.96)	1.60 (0.73–3.51)	1.84 (0.79–4.26)
Severe asthma	4.31 (1.81–10.26)	1.55 (0.62–3.90)	0.55 (0.23–1.33)	0.78 (0.34–1.83)	0.77 (0.36–1.66)

Data are presented as geometric means with 95% confidence intervals in parentheses. LR: living room; BR: bedroom.

The mean age of the SA group was 46 yrs and that of the MA group was 47 yrs. Half of the subjects were male. The mean daily dose of inhaled steroids (BDP or equivalent) for the SA group was 2,232 μg (BA: 2,321 μg, NBSA: 2,143 μg, p=0.53), and for the MA group was 321 μg (p<0.001).

Mean FEV_1 % predicted was significantly lower in the SA group (80.9%) than the MA group (90.2%) (p=0.014). Those with BA had a significantly greater deficit than those with NBSA (BA: 73.5%, NBSA: 88.3%, p=0.015).

Presence of pets in the home

More subjects in the SA group had pets at home than in the MA group; a total of 20 animals (15 dogs and five cats) were in the homes of 16 of the 28 members of the SA group and only nine animals (four dogs and five cats) in the homes of seven of the 28 members of the MA group (Chi-squared: p=0.002). When examining the SA group, proportionately more of the BA homes than NBSA homes had pets (BA: 13 animals in nine homes, NBSA: seven animals in seven homes) but this difference did not achieve statistical significance (Chi-squared: p=0.21).

Skin prick tests

Skin prick testing was declined by two members of the MA group, neither owned pets. In the SA group, all subjects had at least one positive skin prick test, but in the MA group only 14 of the 26 undergoing skin prick testing had one or more positive tests (p<0.001). House dust mite positivity was almost universal in the SA group (27/28) while only 12 of the 26 subjects in the MA group tested positive to this allergen. Dog sensitivity was unusual in the MA group (2/26) in contrast to the SA group (22/28, Chi-squared: p<0.001). Cat positivity was more frequent in the MA group (8/26) than dog sensitivity but did not approach the frequency observed in the SA group (24/28).

Only one of the 26 subjects in the MA group was sensitive to all three allergens, as opposed to 20 of the 28 subjects in the SA group (p<0.0001). (Twelve of the 14 BA positive to each allergen *versus* eight of the 14 in the NBSA (Fisher's exact test: p=0.2).)

Allergen concentrations

Der p *1*. The maximum individual concentrations of *Der p* 1 (table 1) were found in mattress samples from both groups (MA: 200 $\mu g \cdot g^{-1}$, SA(BA): 208 $\mu g \cdot g^{-1}$). The highest site geometric mean was bedding in the SA group (6.91 $\mu g \cdot g^{-1}$) (NBSA: 15.12 $\mu g \cdot g^{-1}$ *versus* BA: 3.54 $\mu g \cdot g^{-1}$).

Can f *1*. The highest individual concentrations (table 1) were found in a living room carpet sample in the MA group (257 $\mu g \cdot g^{-1}$) and a bedroom carpet sample in the SA(BA) group (2,560 $\mu g \cdot g^{-1}$), in each case from a home with a dog. For each site, the concentrations of *Can f* 1 were higher in the SA group than the MA group.

Table 2. – Geometric mean concentrations ($\mu g \cdot g^{-1}$) with 95% confidence intervals of *Can f* 1 and *Fel d* 1 in homes with and without pets

	Homes with a pet	Homes without a pet	p-value
Dog (*Can f* 1)			
Sofa	197.51 (110.66–352.54)	1.92 (1.18–3.13)	<0.0001
Living room carpet	106.15 (47.72–236.10)	2.18 (1.29–3.70)	<0.0001
Mattress	32.62 (14.56–73.10)	0.59 (0.38–0.93)	<0.0001
Bedding	36.04 (13.79–94.16)	0.97 (0.60–1.57)	<0.0001
Bedroom carpet	79.73 (31.21–203.64)	0.96 (0.59–1.59)	<0.0001
Cat (*Fel d* 1)			
Sofa	135.54 (57.06–322.03)	2.04 (1.36–3.05)	<0.0001
Living room carpet	89.86 (29.39–274.71)	1.13 (0.71–1.82)	<0.0001
Mattress	24.71 (7.37–82.88)	0.34 (0.24–0.48)	<0.0001
Bedding	30.99 (12.25–78.36)	0.47 (0.31–0.71)	<0.0001
Bedroom carpet	30.77 (11.39–83.11)	0.51 (0.35–0.75)	<0.0001

Data are presented as geometric means with 95% confidence intervals in parentheses.

Table 3. – Sensitivity and exposure relationships for mite, dog and cat allergens by group and site

	n	Sensitized	Exposed	Exposed and sensitized	% total	p-value
HDM (LR)						
MA	26	12	10	4	15	0.007
SA	28	27	14	14	50	
HDM (BR)						
MA	26	12	9	6	23	<0.0001
SA	28	27	21	21	75	
Dog (LR)						
MA	26	2	1	0	0	<0.0001
SA	28	22	16	13	46	
Dog (BR)						
MA	26	2	1	0	0	<0.0001
SA	28	22	13	11	39	
Cat (LR)						
MA	26	8	2	1	4	0.029
SA	28	24	8	7	25	
Cat (BR)						
MA	26	8	3	1	4	0.19
SA	28	24	5	4	14	

HDM: house dust mite; LR: living room; BR: bedroom; MA: mild asthma; SA: severe asthma. Significance testing by Chi-squared test.

Fel d *1*. The maximum *Fel d* 1 concentrations (table 1) were found in a sofa sample for the SA(NBSA) group (1,380 $\mu g \cdot g^{-1}$) and from a living room carpet sample in the MA group (4,200 $\mu g \cdot g^{-1}$); both of these samples came from homes with a cat.

Allergen concentrations in homes with and without pets. Dust samples from 16 homes with dogs were compared with samples from 40 without a dog, and samples from nine homes with cats were compared with samples from 45 without a cat (table 2). Homes with pets had significantly higher geometric mean concentrations of their respective allergens than households without pets for all sites sampled ($p<0.0001$ for all comparisons).

Sensitivity with exposure

Using the above definitions of sensitivity and significant exposure, the proportion of subjects in each group who were both sensitized and exposed by allergen and site were compared (table 3). The proportion of severe asthmatics both sensitized and exposed to each allergen was significantly greater than those with MA for each site, with the exception of bedroom *Fel d* 1 in cat sensitized individuals where statistical significance was not reached.

Within the SA group, there were no significant differences between the proportions of BA and NBSA subjects both sensitized or exposed, although the increased proportion of BA subjects exposed to significant levels *Can f* 1 in the bedroom approached significance ($p=0.053$) (data not shown, but available on request). The proportions of BA subjects both sensitized and exposed to pet allergens in both the bedroom and living room were greater than those with NBSA, in contrast to house dust mite allergen sensitivity and exposure, where the converse was observed.

Between group comparisons of geometric mean concentrations of allergen in settled dust in those sensitized to that allergen are shown in table 4. In mite-sensitized individuals, the bedroom concentration of *Der p* 1 was significantly higher in the SA group (9.62 $\mu g \cdot g^{-1}$) relative to the MA group (1.74 $\mu g \cdot g^{-1}$) ($p=0.015$). Subgroup examination suggested this association was predominantly a feature of the NBSA subjects, but the difference between the NBSA (12.79 $\mu g \cdot g^{-1}$) and BA (7.23 $\mu g \cdot g^{-1}$) geometric means did not achieve statistical significance ($p=0.46$).

The living room and bedroom concentrations of *Can f* 1 were significantly greater in the dog-sensitized severe asthmatics than the dog-sensitized mild asthmatics (24.04 $\mu g \cdot g^{-1}$ *versus* 0.83 $\mu g \cdot g^{-1}$, $p<0.0001$ and 8.67 $\mu g \cdot g^{-1}$ *versus* 0.26 $\mu g \cdot g^{-1}$, $p<0.0001$). Within the SA group the geometric

Table 4. – Geometric mean concentrations ($\mu g \cdot g^{-1}$) with 95% confidence intervals of allergen in sensitized individuals by site and group

	Mild asthma	Severe asthma	Nonbrittle severe asthma	Brittle asthma
Der p 1				
LR	2.04 (0.54–7.67)	2.2 (1.37–3.51)	2.23 (1.02–4.86)	2.16 (1.27–3.68)
BR	1.74 (0.60–4.94)	9.62 (5.11–18.68)	12.79 (4.58–35.72)	7.23 (3.08–16.99)
Can f 1				
LR	0.83 (0.68–0.99)	24.04 (8.13–71.13)	15.94 (3.11–81.58)	31.96 (7.28–140.39)
BR	0.26 (0.16–0.44)	8.67 (2.97–25.30)	5.75 (1.15–28.69)	17.12 (2.67–49.78)
Fel d 1				
LR	2.25 (0.88–5.79)	4.79 (1.67–13.78)	3.99 (0.83–19.26)	5.04 (1.27–19.99)
BR	1.5 (0.25–8.94)	1.19 (0.45–3.13)	0.88 (0.17–4.41)	1.54 (0.46–5.10)

Data are presented as geometric means with 95% confidence intervals in parentheses. LR: living room; BR: bedroom.

mean concentrations of *Can f* 1 were greater in the BA subgroup, but these differences were not statistically significant for either site (living room: 31.96 $\mu g \cdot g^{-1}$ *versus* 15.94 $\mu g \cdot g^{-1}$, p=0.54, and bedroom: 17.12 $\mu g \cdot g^{-1}$ *versus* 5.75 $\mu g \cdot g^{-1}$, p=0.54).

There were no significant differences in *Fel d* 1 geometric mean concentrations between those sensitized to cat allergen in each group for either site.

Pet allergen exposure in homes without a pet

Seven households had significant levels of pet allergens despite not being home to a pet at the time of the study (data available on request). In one, concentrations of *Can f* 1 were significant in all sites sampled; the household had contained a dog until 6 months prior to the study. Another household had an isolated significant concentration of *Fel d* 1 in dust sampled from the sofa, despite the subject not allowing cats in her home. In this case the sofa had been bought second hand. In the other five homes no obvious cause was identified.

Discussion

This study is the first to show that subjects with SA are exposed to higher levels of domestic allergens to which they are sensitized, compared with subjects with MA. In established asthma, while sensitivity and exposure to allergen are independently associated with disease expression, sensitivity with exposure and *vice versa* is probably of no significance; rather both need to be considered together.

What constitutes exposure and sensitivity remains controversial. Although there is likely to be considerable variability among individuals in both the "threshold" for symptom production [7] and the magnitude of response to the same change in levels of allergen exposure [24], common "significant levels" were adopted (based primarily on published experience dealing with mild-to-moderate asthma [9, 22, 23]) of allergen in settled dust to define an individual′s exposure, and a dichotomous response to skin prick tests to define sensitivity.

Using these definitions, significantly more of the severe asthmatics were both exposed and sensitized to one or more allergens than were the mild asthmatics. This was true for both mite and dog allergen in the living room and bedroom and for cat allergen in the living room. Even if the proposed significant levels were incorrect, the geometric mean concentrations of the relevant allergens were higher in the sensitized severe asthmatics than in the sensitized mild asthmatics.

Pet ownership (particularly dogs) was significantly more common amongst the SA group (54%) compared to the MA group (25%), and all homes that housed a pet contained the relevant allergen at highly significant levels in at least one reservoir. While pet ownership is clearly a very important cause of pet allergen accumulation in the home, high pet allergen levels were also found in some homes that did not contain a pet, emphasizing the need for individual quantification of allergen exposure.

The SA group were highly atopic with 71% multiply sensitized to mite, cat and dog allergen, compared to only 4% in the MA group. Moreover, in SA, sensitization and exposure to multiple allergens was more common than in MA. The relative importance of exposure to each allergen in the clinical activity of asthma in a multiply sensitized subject is unknown. Significant exposure to multiple allergens may be of little more importance than a significant exposure to single allergen, or they could be additive or even multiplicative in effect. If allergen avoidance is to be successful, however, it is likely that avoidance should encompass all allergens to which an individual is sensitized and exposed.

Subgroup analysis of the exposure and sensitivity characteristics of the SA group failed to reveal any significant differences between those with BA, and those with NBSA. This may simply reflect the limited power of such an analysis if significant differences truly exist; the authors would have liked to have been able to include a larger number of subjects with BA, but owing to the rarity of this condition and the need for rigorous and time-dependent characterization procedures, the pool of potential participants at any one time is restricted. Nonetheless, those with BA tended to be sensitized and exposed, and sensitized and exposed to higher concentrations of pet and particularly dog allergen, than those with NBSA, with the converse being true for mite allergen. This suggests that exposure to *Der p* 1 may not be discriminant for these differing phenotypes of SA, but that the presence of a dog in the home and sensitivity/exposure to dog allergen may be an important association with type 1 BA. While this is an attractive and potentially cohesive hypothesis, dog ownership and consequent dog allergen exposure may simply confound the association between this phenotype of SA and increased psychosocial morbidity characteristic of this group of patients [15, 16]. It must also be remembered that in different geographical areas, differing allergens may be of more importance than dog allergen; that is, if the observed association between the type 1 BA phenotype and dog allergen exposure in this study is in fact true, it may be geographically specific.

Although this study has not attempted to address other potentially important factors associated with asthma severity, such as tobacco smoke exposure, occupational exposures, damp housing *etc.*, the authors believe that the issue of allergen avoidance and, in particular, pet allergen avoidance in severe asthma needs to be investigated further. Techniques for reducing mite allergen and pet allergen exposure with the pet *in situ*, have been developed [25]. While these techniques can achieve reductions in allergen levels, it remains uncertain whether they can bestow significant clinical benefits in severe asthma. Protagonists would suggest that such environmental manipulation is the logical next step, but much will depend on the further understanding of other determinants of asthma severity and particularly the nature of the allergen exposure dose–response relationship in subjects with differing asthma severity.

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