

paper, and will act as guarantor. JWK and KJMcK provided advice during the study and commented on the paper.

Funding: None.

Competing interests: None declared.

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(Accepted 5 November 2001)

Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study

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Abstract

Objective To investigate the importance of sensitisation and exposure to allergens and viral infection in precipitating acute asthma in adults resulting in admission to hospital.

Design Case-control study.

Setting Large district general hospital.

Participants 60 patients aged 17-50 admitted to hospital over a year with acute asthma, matched with two controls: patients with stable asthma recruited from the outpatient department and patients admitted to hospital with non-respiratory conditions (inpatient controls).

Main outcome measures Atopic status (skin testing and total and specific IgE), presence of common respiratory viruses and atypical bacteria (polymerase chain reaction), dust samples from homes, and exposure to allergens (enzyme linked immunosorbent assay (ELISA): Der p 1, Fel d 1, Can f 1, and Bla g 2).

Results Viruses were detected in 31 of 177 patients. The difference in the frequency of viruses detected between the groups was significant (admitted with asthma 26%, stable asthma 18%, inpatient controls 9%; $P=0.04$). A significantly higher proportion of patients admitted with asthma (66%) were sensitised and exposed to either mite, cat, or dog allergen than patients with stable asthma (37%) and inpatient controls (15%; $P<0.001$). Being sensitised and exposed to allergens was an independent associate of the group admitted to hospital (odds ratio 2.3, 95% confidence interval 1.0 to 5.4; $P=0.05$), whereas the combination of sensitisation, high exposure to one or

more allergens, and viral detection considerably increased the risk of being admitted with asthma (8.4, 2.1 to 32.8; $P=0.002$).

Conclusions Allergens and viruses may act together to exacerbate asthma.

Introduction

Asthma costs 1-2% of the total health budgets in direct costs, with equally large indirect costs for time lost from work and reduced productivity.^{1,2} Much of these costs come from hospital admissions. Being admitted to hospital with asthma is also an important risk factor for death from the condition.³

Of 450 000 adults admitted yearly with asthma to emergency departments in the United States, an estimated 200 000 were sensitised to mite, cat, or cockroach allergen.⁴ Viral respiratory infections have been associated with most acute exacerbations of wheeze in childhood.⁵ In the early part of each school term there is an increase in hospital admissions for asthma associated with the acquisition of new viruses.⁶ An interaction has been suggested between sensitisation and virus infection in exacerbating asthma in children.⁷ Few studies have been conducted in adults, although there is evidence that viral infections are associated with many exacerbations of asthma.⁸ In experimental studies synergistic effects have been shown between allergens and viruses.^{9,10} No studies have investigated an interaction between sensitisation, exposure to allergens, and viral infections in real life exacerbations of asthma. We therefore determined their relative importance in



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BMJ 2002;324:763-6

Table 1 Participants' personal and housing details. Values are numbers (percentages)

	Patients admitted with asthma (n=61)	Patients with stable asthma (n=58)	Inpatient controls (n=59)
Median age (years)	33.1	34.3	32.9
Male	18 (30)	17 (29)	17 (29)
Current smoker	18 (30)	16 (28)	16 (27)
Past or never smoker	43 (70)	42 (72)	43 (73)
Dog owner	18 (30)	12 (21)	16 (27)
Cat owner	13 (21)	17 (29)	12 (20)
Other pet owner	7 (11)	7 (12)	11 (19)
Double glazing	20 (33)	26 (45)	19 (32)
Gas cooker	36 (59)	37 (64)	34 (58)
Hard floor in bedroom	1 (2)	1 (2)	2 (3)
Central heating	52 (85)	53 (91)	55 (93)
Condensation on bedroom window	31 (51)	31 (53)	29 (49)
Dampness or mould in bedroom	4 (7)	5 (9)	5 (8)

precipitating acute asthma in adults resulting in admission to hospital.

Methods

We matched 60 patients (aged 17-50) admitted to hospital over a year with acute asthma for sex, age, and smoking status with two controls: patients with stable asthma recruited from the outpatient department and patients admitted to hospital with non-respiratory conditions (inpatient controls). We enrolled controls within two weeks of the index case being recruited.

We assessed the participants' atopic status by skin prick testing (house dust mite (*Dermatophagoides pteromyssinus*), cat, dog, cockroach, mixed grasses, trees, *Trichophyton*, *Alternaria*, *Aspergillus*, and negative and positive controls) and measurement of total and specific serum IgE levels. We performed nasal lavage for virology, and we made a home visit within three weeks of recruitment to determine exposure to allergens (environmental questionnaire and collection

of dust samples). We collected dust samples and determined the allergens from the participants' mattresses, bedding, bedroom floors, living room floors, upholstered furniture, and kitchens.¹¹⁻¹⁴

Statistical analysis

We compared the outcome measures across the groups initially by using χ^2 test, one way analysis of variance, and Student's *t* test. Major exposure occurs with Der p 1 ≥ 2 $\mu\text{g/g}$, Fel d 1 ≥ 8 $\mu\text{g/g}$, and Can f 1 ≥ 10 $\mu\text{g/g}$.^{15 16} From these values we divided the population into those exposed or not exposed to high levels of allergens. We carried out a further analysis of the risk factors for admission with asthma in the acute and stable asthma groups with logistic regression. Initially we assessed risk factors by univariate analysis. We then tested variables in a multivariate analysis, combining the relevant variables to control for the effect of each explanatory variable on the other variables studied.

Results

We recruited 178 patients: 61 admitted with asthma, 58 with stable asthma, and 59 inpatient controls. We matched 57 of the patients admitted with asthma with two controls. One patient admitted with asthma had a control with stable asthma only, two an inpatient control only, and one no suitable controls. Table 1 lists the participants' personal and housing details.

Sensitisation to inhalant allergens

Significant differences were observed between the three groups in the frequency of positive skin tests for dust mite, cat, dog, and grass allergens but not for other allergens (table 2). No differences were found between patients admitted with asthma and those with stable asthma, and the observed difference between the groups was due to the lower proportion of inpatients

Table 2 Sensitisation to allergens, evidence of viral infection, and concentration of total and specific serum IgE to allergens in three groups of patients. Values are numbers (percentages) unless stated otherwise

	Patients admitted with asthma (n=61)	Patients with stable asthma (n=58)	Inpatient controls (n=59)	P value
Sensitisation to allergens	n=59	n=58	n=59	
House dust mite	39 (66)	33 (57)	22 (37)	0.006
Cat	34 (58)	29 (50)	9 (15)	<0.001
Dog	24 (41)	22 (38)	3 (5)	<0.001
Cockroach	5 (9)	6 (10)	8 (14)	0.67
Mixed grasses	35 (59)	30 (52)	20 (34)	0.02
Trees	8 (14)	11 (19)	5 (9)	0.26
<i>Alternaria</i>	11 (19)	8 (14)	2 (3)	0.03
<i>Aspergillus</i>	6 (10)	5 (9)	2 (3)	0.33
<i>Trichophyton</i>	3 (5)	5 (9)	4 (7)	0.34
Positive skin prick test result	51 (86)	43 (74)	32 (54)	<0.001
1 allergen	8 (14)	7 (12)	14 (24)	<0.001
2 allergens	16 (27)	8 (14)	6 (10)	
≥ 3 allergens	27 (46)	28 (49)	12 (20)	
Detection of viruses	n=61	n=57	n=59	
Picornavirus	6 (10)	2 (4)	2 (3)	0.20
Coronavirus	10 (16)	8 (14)	3 (5)	0.18
Any polymerase chain reaction	16 (26)	10 (18)	5 (9)	0.038
Total and specific serum IgE level (kAU/l; geometric mean, 95% CI)				
Total IgE	253.7 (170.9 to 376.5)	123.7 (75.7 to 202.2)	63.2 (38.8 to 103.0)	<0.001
House dust mite	3.3 (1.7 to 6.4)	2.7 (1.4 to 5.0)	1.2 (0.7 to 2.2)	0.02
Cat	2.5 (1.4 to 4.7)	1.7 (0.9 to 3.0)	0.6 (0.4 to 1.0)	<0.001
Dog	1.6 (0.9 to 2.8)	1.5 (0.9 to 2.5)	0.6 (0.4 to 0.8)	<0.001
Cockroach	0.5 (0.4 to 0.6)	0.4 (0.3 to 0.5)	0.4 (0.3 to 0.5)	0.63

being sensitised. Similarly, total and specific IgE levels to mite, cat, and dog allergens were significantly higher in both groups of patients with asthma than in patients admitted with non-respiratory conditions (admitted *v* inpatient controls: total IgE, mean difference 4.3-fold, 95% confidence interval 2.4 to 7.6, $P < 0.001$; specific IgE to mite, 2.5, 1.2 to 5.0, $P = 0.01$; specific IgE to cat, 4.2, 2.1 to 8.3, $P < 0.001$; specific IgE to dog, 2.9, 1.6 to 5.2, $P = 0.001$). Although total serum IgE levels were higher in patients admitted with asthma than in those with stable asthma (53%, 29% to 96%, $P = 0.04$), there were no significant differences between specific IgE levels.

Detection of viruses

Viruses were detected in 31 of 177 patients (17%): picornaviruses in 10 and coronavirus in 21. No other viruses or atypical bacteria were detected. A significant difference was found in the frequency of viral detection between the three groups (admitted with asthma 26.2%, stable asthma 17.5%, inpatient controls 8.5%; $P = 0.038$) (table 2).

Exposure to allergens

Patients admitted with asthma had significantly higher levels of Der p 1 in their mattress and bedding, Fel d 1 levels in mattress, and Can f 1 in bedroom floor and mattress than patients with stable asthma. Patients admitted with asthma also had significantly higher levels of Der p 1 in both mattress and bedding than inpatient controls. No differences were observed between patients with stable asthma and inpatient controls. Bla g 2 levels were low and not different between groups.

Combinations of sensitisation, exposure to allergens, and viral detection

A significantly higher proportion of patients admitted with asthma (66%) were sensitised and exposed to either mite, cat, or dog allergens than patients with stable asthma (37%) and inpatient controls (15.1%; $P < 0.001$). A highly significant difference was observed between the groups for the combination of sensitisa-

tion and exposure to high levels of sensitising allergen and viral detection.

Risk factors for admission with asthma

We carried out further analysis of the risk factors for admission in patients with acute and stable asthma by using logistic regression. Sensitisation to each or any of the allergens by itself was not significantly associated with hospital admission (table 3). However, being both sensitised and exposed to high levels of dust mite allergen was significantly associated with hospital admission, and strong trends were observed for both sensitisation and exposure to high levels of cat and dog allergens. Sensitisation and exposure to any one or more allergens was significantly associated with hospital admission (odds ratio 3.2, 95% confidence interval 1.4 to 7.1). Detection of viruses alone was not significantly associated with admission for asthma (table 3). However, of 16 patients admitted with asthma with detectable viruses, 14 were also sensitised and exposed to high levels of allergen, compared with only 3 of 10 with stable asthma. The combination of sensitisation and high exposure to one or more allergens and detection of viruses was a strong and significant associate of admission for asthma.

When sensitisation, exposure to allergens, and detection of viruses were controlled for, being both sensitised and exposed to allergens was an independent associate of admission with asthma (2.3, 1.0 to 5.4). However, the combination of sensitisation and high exposure to one or more allergens and detection of viruses increased the risk of admission with asthma (8.4, 2.1 to 32.8).

Discussion

Exposure to allergens has been related to disease severity.¹⁷⁻¹⁹ Patients with severe asthma were significantly more often sensitised and exposed to high levels of allergens to which they were allergic than patients with mild disease.¹⁸ Thus for symptoms to occur there must be both sensitisation and exposure.

Table 3 Concentration of allergens ($\mu\text{g/g}$ of dust) to house dust mite, dog, cat, and cockroach from six sites in three groups of patients. Values are geometric means (95% confidence intervals) unless stated otherwise

Allergen	Location sampled	Patients admitted with asthma (n=61)	Patients with stable asthma (n=58)	P value (admissions <i>v</i> stable patients)	Inpatient controls	P value (admissions <i>v</i> inpatients)
Der p 1	Living room floor	1.10 (0.67 to 1.82)	0.73 (0.48 to 1.12)	0.722	0.68 (0.45 to 1.03)	0.459
	Sofa	1.75 (0.89 to 2.44)	1.05 (0.67 to 1.67)	0.666	0.76 (0.53 to 1.11)	0.102
	Kitchen floor	0.64 (0.42 to 0.98)	0.40 (0.27 to 0.57)	0.238	0.39 (0.28 to 0.54)	0.178
	Bedroom floor	1.31 (0.85 to 2.02)	0.73 (0.46 to 1.16)	0.188	0.74 (0.47 to 1.15)	0.079
	Mattress	5.02 (2.96 to 8.51)	1.80 (1.05 to 3.10)	0.024	2.38 (1.49 to 3.81)	0.05
	Bedding	5.02 (2.96 to 8.51)	1.80 (1.05 to 3.10)	0.024	2.38 (1.49 to 3.81)	0.05
Can f 1	Living room floor	7.69 (3.72 to 15.90)	3.22 (1.54 to 6.75)	0.130	4.63 (2.18 to 9.82)	0.429
	Sofa	9.98 (5.10 to 19.53)	3.31 (1.66 to 6.59)	0.097	6.27 (3.21 to 12.27)	0.362
	Kitchen floor	2.57 (1.36 to 4.87)	1.49 (0.71 to 3.13)	0.353	1.68 (0.87 to 3.23)	0.438
	Bedroom floor	3.17 (1.70 to 5.91)	1.15 (0.58 to 2.28)	0.05	1.57 (0.78 to 3.18)	0.192
	Mattress	2.48 (1.27 to 4.82)	1.07 (0.60 to 1.90)	0.138	1.33 (0.75 to 2.38)	0.295
	Bedding	3.32 (1.72 to 6.41)	1.15 (0.61 to 2.16)	0.05	1.60 (0.82 to 3.13)	0.210
Fel d 1	Living room floor	2.45 (1.17 to 5.14)	3.98 (1.67 to 9.50)	0.663	3.26 (1.61 to 6.63)	0.940
	Sofa	6.68 (2.92 to 15.29)	7.47 (3.17 to 17.63)	0.778	6.12 (3.13 to 11.97)	0.458
	Kitchen floor	1.22 (0.51 to 2.90)	1.39 (0.62 to 3.12)	0.729	1.13 (0.51 to 2.50)	0.263
	Bedroom floor	1.76 (0.79 to 3.91)	1.04 (0.46 to 2.35)	0.258	1.88 (0.90 to 3.91)	0.689
	Mattress	2.39 (1.13 to 5.09)	0.89 (0.40 to 1.97)	0.049	1.55 (0.74 to 3.22)	0.181
	Bedding	2.42 (1.06 to 5.53)	1.14 (0.50 to 2.61)	0.098	1.90 (0.90 to 4.02)	0.375

What is already known on this topic

Studies on segmental allergen challenge of the lung and experimental rhinovirus infection show synergistic effects between allergens and respiratory virus infection

No studies have investigated an interaction between sensitisation, exposure to allergens, and virus infections in real life exacerbations of asthma

What this study adds

Allergens and viruses may act together to exacerbate asthma, indicating that domestic exposure to allergens acts synergistically with viruses in sensitised patients, increasing the risk of hospital admission

Strategies to reduce the impact of asthma exacerbations in adults should include interventions directed at both viruses and reducing exposure to allergens

Viral infection

Viral infection was noticeably less common in adults admitted to hospital with acute asthma than in children or adults having asthma exacerbations in the community.⁵⁻⁸ However, viral infection represents a significant risk factor in those patients who are also both sensitised and exposed to allergens. Our data suggest that patients with asthma are more susceptible to viral infections than patients without asthma but that such an infection may not necessarily induce deterioration in asthma requiring hospital admission. Only 16 of our patients with acute asthma had a positive polymerase chain reaction results for a respiratory virus. This is in contrast to several previous studies in children from our group, which have shown a strong relation between virus infection and exacerbations of asthma.⁵ Twenty two of the our patients who were admitted reported symptoms which they attributed to a cold before admission, but they had negative polymerase chain reaction result for virus. These symptoms may have been due to an allergic response that was mistaken for infection. They could also be true viral infections that were not detected.

Respiratory virus infection and allergic inflammation

Several experimental studies have shown a synergistic interaction between respiratory virus infection and allergic inflammation. Histamine responsiveness and epithelial eosinophils increased during the viral infection but only persisted into the convalescent period in the patients with asthma.²⁰ Grunberg et al challenged patients with atopic asthma with rhinovirus or placebo.²¹ In the group inoculated with rhinovirus there was no significant change in lung function but there was an increase in bronchial hyper-reactivity and interleukin 8, which correlated with the severity of the cold. In a study of patients with allergic rhinitis who were sensitised to ragweed, after infection with rhinovirus 16 the patients developed nearly a threefold increased non-specific and specific airway responsiveness during the acute viral infection, with an increased probability of a late asthmatic reaction with ragweed challenge for up to four weeks after the infection.²²

Conclusions

Allergens and viruses may act together to exacerbate asthma, indicating that domestic exposure to allergens acts synergistically with viruses in sensitised patients, increasing the risk of hospital admission. In the absence of the effective strategies to control viruses, attention should be paid to reducing exposure to allergens.

We thank Martin Chapman, Martin Brutsche, Helen Marolia, Jill Fletcher, Mandy Mycock, Mark Craven, and Greg Cain for their help, and Julie Morris and Stephen Francis for statistical advice.

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Funding: RMG was funded by a scholarship award from the UCB Institute of Allergy, award number 95320. AC is the recipient of the National Asthma Campaign senior clinical research fellowship.

Competing interests: None declared.

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