

Time course of onset of sensitization to common and occupational inhalants in apprentices

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Background: Incident sensitization to common allergens in the setting of sensitization to an occupational allergen has not been described.

Objective: Our aim was to determine the risk and timing of development of sensitization to common allergens in subjects with incident sensitization to a work-related allergen.

Methods: Data from a cohort of 769 apprentices in animal-health technology, pastry making, and dental hygiene were used. Skin prick tests to work-related allergens (laboratory animal, flour, and latex) and common allergens (mites, molds, pets, and pollen) were administered at baseline and at up to 3 subsequent annual visits. Risk ratios (RRs) and 95% CIs were calculated.

Results: Eighty-three subjects had sensitization to a work-related allergen. Four (4.8%) subjects became sensitized to common and then occupational allergens. Nine (10.8%) subjects had sensitization to a common allergen after sensitization to a work-related allergen. In 20 (24.1%) subjects new sensitizations to specific and common allergens were detected simultaneously. Fifty subjects remained free from new sensitization to occupational allergen during development of sensitization to common allergens. An increased risk of development of sensitization to molds (RR = 3.49) and pets (RR = 2.51) was found in subjects with incident sensitization to occupational allergens relative to the risk in subjects without sensitization.

Conclusion: New sensitization to common aeroallergens is frequent in subjects not previously exposed to work-related allergens; it often occurs around the same time as sensitization to work-related agents. Subjects with new occupational sensitization are at a greater risk of development of sensitization to common aeroallergens than subjects without sensitization. (*J Allergy Clin Immunol* 2003;111:807-12.)

Key words: IgE-mediated hypersensitivity, occupational exposure, occupational asthma, asthma

Sensitization to allergens present in the workplace is a common cause of asthma.^{1,2} Atopy has been reported in various studies as a determinant of skin sensitization to occupational high-molecular-weight agents.³ It is not known whether sensitization to an allergen present in the workplace is by analogy a risk factor for sensitization to common aeroallergens. One could indeed hypothesize that

Abbreviation used
RR: Relative risk

the mechanism for associated sensitizations to common and occupational allergens could be related to T-cell recruitment after occupational exposure to proteinaceous substances. This could serve as a priming event, leading to the recruitment of other T cells specific for the common aeroallergens. We therefore do not know whether sensitization to common aeroallergens precedes or follows sensitization to occupational allergens. In the present work we aimed to examine whether subjects who acquire sensitization to high-molecular-weight work-related allergens are more likely to become sensitized to common inhalants than subjects who do not acquire such sensitization. We also sought to examine the timing of these 2 events in subjects in whom sensitization to a specific work-related allergen developed. We hypothesized that there is an increased risk of sensitization to common allergens in subjects who have sensitization to an occupational allergen.

METHODS

Subjects

A cohort of 769 apprentices (417 in animal-health technology, 230 in pastry making, and 122 in dental-hygiene technology) was constituted by recruiting students from teaching institutions in Quebec, Canada, in a process described elsewhere.⁴ The subjects were recruited on entering their training programs and considered eligible if they had not been exposed to the relevant work-related allergen for 3 months or more in the course of an apprenticeship. Those in animal-health technology were reassessed at 20, 32, and 44 months; those in dental-hygiene technology at 20 and 32 months; and those in pastry making at 8 and 16 months.

Skin testing

At each visit, skin tests were done with the prick method⁵ by using 11 common inhalants: mixed tree, mixed grass, and ragweed pollen; *Alternaria*, *Aspergillus*, and *Hormodendrum* species; feathers; *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*; and cat and dog dander (Omega, Montreal, Canada). We also used the following occupational allergens: urinary proteins from rat, mouse, and rabbit (Pharmacia Allergon AB, Angelholm, Sweden); hamster, guinea pig, and rabbit dander (Omega); mixed flours, wheat, and bran flour; and latex (Omega and Stallergenes, Institut Pasteur, Paris, France). Mite extracts and cat danders were standardized. All extracts were glycerinated. Histamine phosphate (1/200 g/mL) was used as a positive control, and diluent (glycerine 50%) was used as a negative control. The largest and perpendicular diam-

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			Sensitization to common allergens				
			Present				Absent at the end of the study
			Visit 1 baseline	Visit 2	Visit 3	Visit 4	
Sensitization to occupational allergens	Present	Visit 1 baseline					
		Visit 2		G2	G3		G4
		Visit 3			G2		
		Visit 4		G1		G2	
	Absent at the end of the study			G5			G6

FIG 1. Description of relevant groups according to occurrence and timing of sensitization.

eters of the wheal were assessed 10 to 15 minutes after administering the antigen by means of the prick method with a 25-gauge needle. A positive reaction was defined as a wheal (the largest wheal diameter) of 2 mm or larger in the absence of a positive reaction to the diluent and a positive reaction to histamine phosphate accompanied by a flare. A threshold of wheal reaction of 2 mm was used because this has been advocated by Pepys and Bernstein with the prick method, as reviewed by Bousquet,⁶ although most often a threshold of 3 mm is selected. Precautions were taken to minimize variability in skin test results, as described previously.⁷ Subjects had not taken antihistamine preparations for at least 3 days before testing. The survey was carried out from October to May and therefore not in the grass and ragweed pollen seasons.

Definition of incident sensitization

Several sizes of skin reactions were considered (ie, ≥ 2 mm, ≥ 3 mm, ≥ 4 mm, and ≥ 5 mm). For the purpose of the analysis, the common allergens were regrouped into 4 categories: pollens, molds, mites, and pets. New sensitization to a common or occupational allergen was defined as a negative skin prick test response at the initial visit and incidence of a skin reaction at a subsequent visit with persistence thereafter to compensate for possible misclassification of positive and negative reactions and to ensure that the sensitization phenomenon was persistent (ie, in the case of the onset of a ≥ 3 -mm wheal at a follow-up visit, the reaction had to be ≥ 3 mm at a later visit to represent a case of sensitization). Sensitization to a program-related allergen was defined as the onset of a positive skin test reaction to one or more of the occupational inhalants specific to the program. The temporal association between the onset of sensitization to a program-specific allergen and to common inhalants was examined according to the scheme described in Fig 1 and Table I, which identifies 6 relevant groups.

The number of subjects sensitized to a common allergen after a specific allergen was calculated as the sum of those sensitized at a subsequent visit plus one half of those detected as newly sensitized at the same visit on the basis of the assumption that half of the subjects in group 2 (Fig 1 and Table I) had sensitization to common inhalants after becoming sensitized to an occupational allergen,

which is a usual procedure in epidemiologic studies in which the exact date of occurrence of an event between 2 visits is not available.

Statistical analysis

The incidence of sensitization to each category of common inhalant in subjects with incident sensitization to an occupational allergen and in those without sensitization was obtained. Calculations of relative risks (RRs) and associated 95% CIs for sensitization to common inhalants in subjects with and without incident sensitization to occupational allergens were performed. Statistical tests were done with Epi Info 6 for DOS (CDC, Atlanta, Ga).

This project was approved by the ethics committee of Hôpital du Sacré-Coeur de Montréal, and the subjects provided written consent.

RESULTS

Among the 769 subjects included in this study, 698 participated in at least one of the follow-up visits; 690 had interpretable skin test results and have been included in the analysis. There were 394 subjects in the animal-health program, 186 in the pastry-making program, and 110 in the dental-hygiene program. The numbers and characteristics of the participants present during follow-up visits have been described in a previous publication.⁷ Briefly, 85% of subjects were female, 55.2% were atopic, and the mean $\pm$ SD age was 22.3 ± 7.3 years; these figures were similar for the 3 programs. The prevalence figures of sensitization to common inhalants at the initial visit are shown in Table II. In apprentices exposed to laboratory animals, the incidences of sensitization to occupational allergens and mites were 22% and 12%, respectively.⁸ Sensitization to an occupational allergen was more common in apprentices exposed to laboratory animals (7.9% per person-year), followed by apprentices in baking (4.2% per person-year) and apprentices in dental hygiene exposed to latex (2.5% per person-year).⁷

TABLE I. Occurrence and timing of sensitization

Group	Sensitization to ≥ 1 occupational allergen	Incidence of sensitization to common allergens in relation to incidence of occupational allergens	Sensitization to ≥ 1 common allergen
1	Yes, incident	Before	Yes, incident
2	Yes, incident	Same time	Yes, incident
3	Yes, incident	After	Yes, incident
4	Yes, incident	—	No
5	No	—	Yes, at entry
6	No	—	No

TABLE II. Prevalence of sensitization to common inhalants at the initial visit according to wheal diameters

Inhalants	Wheal diameter			
	≥ 2 mm	≥ 3 mm	≥ 4 mm	≥ 5 mm
Grass pollens (%)	27.1	25.1	21.7	18.4
Ragweed pollen (%)	29.7	28.6	25.3	22.8
Tree pollen (%)	7.8	5.5	2.2	0.9
<i>D farinae</i> (%)	40.3	35.5	27.5	24.0
<i>D pteronyssinus</i> (%)	36.8	30.6	25.1	20.8
Cat dander (%)	18.2	14.9	9.1	6.0
Dog dander (%)	15.5	10.8	5.1	3.8
<i>Alternaria</i> species (%)	8.7	8.0	5.5	4.0
<i>Aspergillus</i> species (%)	6.6	4.7	0.9	0.2
<i>Hormodendrum</i> species (%)	10.2	7.5	3.3	1.3

TABLE III. Distribution of incident cases of sensitization to common allergens with respect to time of occurrence of sensitization to occupational allergens on the basis of skin test wheal diameter

Skin test wheal diameter	Group 1	Group 2	Group 3	Group 4	Total
≥ 2 mm	8	38	9	68	123
≥ 3 mm	4	20	9	50	83
≥ 4 mm	4	12	2	44	62
≥ 5 mm	1	11	2	31	45

Four groups are defined according to the temporal scheme shown in Fig 1: *group 1*, sensitization to a common and then to an occupational allergen; *group 2*, sensitization to a common and to occupational allergens detected at the same time; *group 3*, sensitization to a common allergen after sensitization to an occupational allergen; *group 4*, incident sensitization to an occupational allergen without sensitization to a common allergen.

Table III shows the timing of common sensitization in subjects who had a new specific sensitization according to the diameter of skin test reactions (≥ 2 , ≥ 3 , ≥ 4 , or ≥ 5 mm). For the most commonly accepted criterion of positivity (ie, ≥ 3 mm), we found a total of 83 subjects with incident sensitization to an occupational allergen. Considering the 3-mm or larger skin reaction threshold, 4 (4.8%) of 83 students developed skin reactivity to one or another of the common inhalants before they did for the program-specific allergen, 20 (24.1%) developed both program-specific sensitization and sensitization to common inhalants during the same follow-up interval, 9 (10.8%) became sensitized to a common allergen after acquiring skin reactivity to an occupational allergen, and 50 (60.2%) did not develop skin reactivity to a common allergen during the follow-up period. Therefore there were 33 (39.8%) of 83 instances of incident sensitization to at least one common allergen in subjects who had sensitization to occupational allergens. Of these 33 subjects, 20 (60.6%) demonstrated new sensitization at the same visit. There were 25 incident cases of sensitization to cat; of these, only 3 subjects had acquired a cat for the first time during the same period, 5

subjects had acquired a cat after being sensitized, and 17 subjects had no cat. For dogs, 20 subjects had sensitization, only one of whom reported having acquired a dog in the preceding time interval. Of the 21 incident cases of sensitization to flour with a reaction of 2 mm or larger, 11 (52%) were either prevalent or incident cases of sensitization to grass pollens.

Tables IV and V show subjects in groups 1 to 6. The number of subjects in groups 2 through 6 were used to calculate the risk of becoming sensitized to each of the 4 categories of common inhalants once a subject had shown skin reactivity to a program-specific allergen. The results are listed for the combined 3 programs (Table IV) and for the animal-health group alone (Table V), which was the largest group. At the threshold of 3 mm or larger, the subjects with new occupational sensitization had an increased risk of development of sensitization to molds and pets. When examining only the group of subjects without any reaction to skin prick tests at baseline ($n = 336$ in the whole group, not shown in Table IV), we found higher risks for development of sensitization to mites (RR = 3.2; 95% CI, 1.2-8.6) and pollens (RR = 17.1; 95% CI, 5.7-

TABLE IV. Distribution of all subjects (n = 690) according to the incidence and timing of sensitization to common and occupational allergens (groups 1-6) and RRs of sensitization to common inhalants in subjects with incident sensitization to occupational allergens compared with those without sensitization

		Group						RR (95% CI)	P value*
		1	2	3	4	5	6		
≥2-mm wheal diameter									
	Mites	3	10	3	35	48	355	1.48 (0.73-2.99)	.27
	Molds	3	20	4	50	37	507	2.61 (1.58-4.31)	<.001
	Pets	4	17	3	42	40	465	2.27 (1.27-4.07)	.007
	Pollen	0	7	1	46	23	400	1.40 (0.55-3.59)	.48
≥3-mm wheal diameter									
	Mites	2	5	2	24	41	409	1.52 (0.56-4.13)	.42
	Molds	0	14	2	39	25	560	3.49 (1.87-6.51)	<.001
	Pets	3	8	3	33	35	528	2.51 (1.20-5.26)	.015
	Pollen	0	3	1	29	18	362	1.33 (0.34-5.15)	.68
≥4-mm wheal diameter									
	Mites	1	5	0	22	31	527	1.47 (0.36-5.96)	.59
	Molds	0	6	1	37	17	629	3.19 (1.26-8.09)	.01
	Pets	2	5	2	30	30	596	2.28 (0.86-6.07)	.09
	Pollen	0	2	1	22	16	476	2.39 (0.61-9.34)	.21
≥5-mm wheal diameter									
	Mites	0	5	0	17	24	527	2.31 (0.57-9.39)	.23
	Molds	0	2	0	27	15	674	1.60 (0.23-11.05)	.63
	Pets	1	4	0	22	24	649	2.23 (0.56-8.95)	.25
	Pollen	0	1	1	13	14	504	3.53 (1.11-17.84)	.02

See Fig 1 and text for details on the definition of the groups: $RR = \frac{(\text{group 2/2} + \text{group 3})/(\text{group 2/2} + \text{group 3} + \text{group 4})}{\text{group 5}/(\text{group 5} + \text{group 6})}$.

* χ^2 Test or Fisher exact test.

TABLE V. Distribution of subjects in animal-health technology (n = 394) according to the incidence and timing of sensitization to common and occupational allergens (groups 1-6) and RRs of sensitization to common inhalants in subjects with incident sensitization to occupational allergens compared with those without sensitization

		Group							
	Allergen	1	2	3	4	5	6	RR (95% CI)	P value*
≥2-mm wheal diameter									
	Mites	3	8	3	29	40	167	1.01 (0.48-2.12)	.98
	Molds	3	15	4	43	14	262	2.69 (1.62-4.46)	<.001
	Pets	4	12	3	35	25	232	1.81 (0.97-3.38)	.07
	Pollen	0	7	1	41	20	204	1.00 (0.39-2.53)	.98
≥3-mm wheal diameter									
	Mites	2	5	2	19	27	201	1.41 (0.52-3.81)	.50
	Molds	0	11	2	35	7	297	4.12 (2.27-7.47)	<.001
	Pets	3	6	2	27	17	275	2.30 (1.01-5.32)	.05
	Pollen	0	2	1	27	16	232	1.06 (0.27-4.10)	.93
≥4-mm wheal diameter									
	Mites	1	4	0	19	18	241	1.33 (0.34-5.29)	.68
	Molds	0	6	1	31	6	331	4.25 (1.87-9.67)	<.001
	Pets	2	5	2	25	18	312	2.25 (0.87-5.84)	.10
	Pollen	0	2	1	20	14	256	1.66 (0.43-6.45)	.47
≥5-mm wheal diameter									
	Mites	0	4	0	16	18	265	1.67 (0.42-6.71)	.47
	Molds	0	2	0	25	5	355	2.47 (0.40-15.38)	.34
	Pets	1	2	0	21	12	340	1.31 (0.19-8.98)	.78
	Pollen	0	1	1	13	12	275	1.65 (0.23-11.64)	.61

See Fig 1 and text for details on the definition of the groups: $RR = \frac{(\text{group 2/2} + \text{group 3})/(\text{group 2/2} + \text{group 3} + \text{group 4})}{\text{group 5}/(\text{group 5} + \text{group 6})}$.

* χ^2 Test or Fisher exact test.

51.7). In the animal-health group molds and pets were also the only 2 categories of aeroallergens for which sensitization was significantly more frequent than in subjects without incident occupational sensitization. With skin tests of 4 mm or larger, the RR for sensitization to molds was significantly increased in the whole group and in the animal-health group. Using the criterion of 5 mm or larger, we observed that subjects had an increased risk of becoming sensitized only to pollen.

DISCUSSION

The parallel time course of sensitization to common inhalants and occupational high-molecular-weight agents in exposed apprentices has not, to our knowledge, been described. We found the following over the maximum 44-month observation period: (1) once sensitization to an occupational high-molecular-weight agent occurs, there was often incident sensitization to common allergens as well (33/83 [39.8%] subjects); (2) incident sensitization to common and occupational inhalants was most often documented at the same visit (20/33 [60.6%] subjects); and (3) for the whole group and for the animal-health group, there was an increased risk for sensitization to molds and pets in subjects with incident sensitization to occupational allergens.

As mentioned, one could hypothesize that the mechanism for associated sensitizations to common and occupational allergens could be related to T-cell recruitment after occupational exposure to proteinaceous substances, with the latter being considered a priming situation. Also, cross-reactivity or the existence of shared epitopes between certain proteins could partially explain this observation. For animal-derived allergens, it has been reported that there is some sequence homology between chain 1 of Fel d 1, a major cat allergen, and rabbit uteroglobulin⁹ and mouse salivary protein.¹⁰ Similarly, grass-derived, latex-derived, and pollen-derived antigens share common allergenic properties.^{11,12} These phenomena can explain why we found shared reactivity to laboratory animal-derived and pet-derived allergens on the one hand, as well as to flour-derived and grass pollen-derived allergens on the other hand.

We found a significant number of cases of sensitization to cat and dog dander, as well as to occupational allergens, over a 44-month follow-up period. The Tucson epidemiologic survey has revealed an overall increase in the prevalence of at least one reaction to 5 common inhalants from 39.1% to 50.7% over a mean follow-up period of 8 years.¹³ The prevalence of positive skin prick test responses significantly increased in 5 years from 17.5% to 24.7% in 223 subjects.¹⁴ An increase in the prevalence of skin test positivity of 4% was found in 114 children tested 2 years apart.¹⁵ In a 6-year follow-up study of 408 Danish children and adolescents aged 7 to 17 years, point prevalences of atopy (defined as at least one positive skin test reaction) increased from 26% to 44%.¹⁶ Finally, in a survey that included 165 asthmatic children monosensitized to an allergen and seen 2 to 10 years later, 44% became polysensitized.¹⁷

The fact that the animal-health group was the largest in this cohort might account for the observed tendency toward a significant risk for sensitization to pets in the whole group. We do not have a reasonable explanation for the increased risk of sensitization to molds in the animal-health program, but one possibility could be that the risk for sensitization to mold was more likely to be higher in a group with only 12.8% sensitized apprentices to this allergen at baseline. Indeed, to be considered a new case of sensitization to one of the 4 groups of common aeroallergens, subjects had to have negative skin prick test responses at the initial visit and positive reactions after entering their vocational programs. Therefore incident sensitization was more likely to occur to molds than to pollens or mites, considering that about 36.5% of subjects in the animal-health program were already sensitized to the latter allergens at entry. Moreover, sensitization to molds is generally a reflection of sensitization to other common inhalants, with sensitization to mold alone being extremely rare.¹⁸

In our definition of incident sensitization, changes had to be consistent in time; that is, once a subject had a positive skin reaction to either a common or a specific allergen, the reactivity had to be found at a later visit for the sensitization to be considered present. This ensured a true conversion from negative to positive results, rather than a mere variation in skin response.

When new sensitizations to both common and work-specific allergens were detected at the same visit, it was not possible to assess which appeared first. Had our initial study design included skin reactivity assessments more frequently than once per year, the timing of the 2 events could have been described more precisely. This has also prompted us to consider that half of the apprentices in group 2 became sensitized to common inhalants after becoming sensitized to their program-specific allergen and to estimate the RRs accordingly.

Development of sensitization to pets is unlikely to be due to new exposure to cats and dogs at home. Indeed, only 3 of the subjects who became sensitized to cat and 1 of the subjects who became sensitized to dog had acquired a cat, dog, or both in the same or a previous time period. It is known that cat and dog allergens are becoming almost ubiquitous.¹⁹

Gautrin et al²⁰ have previously shown that skin reactivity to pets represents a determinant for development of probable occupational asthma to laboratory animals, as determined by the development of specific immunologic reactivity and bronchial hyperresponsiveness to methacholine. Those findings and those from the current study point to the relevance of assessing sensitization to common allergens for surveillance programs of occupational sensitization because sensitization to common inhalants can be regarded as a concomitant marker for allergic sensitization to occupational agents. Whether becoming sensitized to common allergens concomitantly or after acquiring sensitization to a specific work-related antigen is associated with a greater risk of development of occupational asthma is not known, and further studies are warranted.

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