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ORIGINAL ARTICLES

Occupational Allergic Disease in Cereal Workers by Stored Grain Pests

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ABSTRACT

It is well known that workers occupationally exposed to grain dust have a high prevalence of respiratory symptoms, but their pathogenesis remains obscure when sensitization to cereal flour cannot be demonstrated. Storage mites, tenebroids, and cockroaches are stored-grain pests found in grain and cereal products frequently in our area, where the cereal industry is the most important industry. An epidemiological analysis of sensitization to these stored-grain pests was performed on 4379 patients residing in an area of cereal industries. Fifty grain workers were selected for in vivo diagnostic tests with nine genera of mites, *Tenebrio molitor* and *Blatta orientalis*. Specific IgE antibodies to the extracts were demonstrated by prick tests and RAST. Association between respiratory symptoms and occupational exposure was confirmed by challenge tests (specific and methacholine). The prevalence of mite sensitization in the total sample studied (4379) was 18.96% (SEM 0.58, 95% CI 16.93-19.19). The prevalence of sensitization to storage mites among mite-sensitive patients was 11.88% (SEM 1.15, 95% CI 9.63-14.3). Among the 50 selected patients the most frequent

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sensitization was that to *Dermatophagoides pteronyssinus* (58%), followed by *Dermatophagoides farinae* (48%), *Lepidoglyphus destructor* and *Tyrophagus putrescentiae* (38%), *Blomia kulagini* (34%), and *Acarus siro* and *Chortoglyphus arcuatus* (24%). In addition, 22% of the patients presented negative prick tests and RAST for *Dermatophagoides* species with positive test to storage mites. Fifty percent of the 50 patients were sensitized to *Tenebrio molitor* (SEM 0.7, CI 95% 36–64), and 36% to *Blatta orientalis* (SEM 0.67, CI 95% 23–49). The identification of mites, tenebroids, and cockroaches in dust samples yields useful data for the diagnosis of our patients.

INTRODUCTION

Occupational exposure to arthropods is an important cause of allergic disease (1). Storage mites, *Tenebrio molitor* and *Blatta orientalis*, are stored-grain pests found in grain and cereal products common in our area, in which the cereal industry of wheat, rye, and barley is the most important industry.

Allergy to storage mites in the form of bronchial asthma and allergic rhinoconjunctivitis has been reported among farmers (2–4), bakers, and grain elevator workers (5,6). The most common storage mites in our area belong to the family Glycyphagidae (genera *Lepidoglyphus*, *Glycyphagus*, and *Blomia*), Acaridae (genera *Tyrophagus*, *Acarus*, *Suidasia*, and *Aleuroglyphus*) and Chortoglyphidae (genus *Chortoglyphus*) (6–9). There is increasing interest in the allergenicity of these mites because different investigators have found little or no cross-reactivity among *Dermatophagoides* spp. and storage mites (10–15), suggesting that this lack of cross-reactivity may imply important clinical and therapeutic consequences for individuals sensitized to storage mite allergens.

T. molitor is a member of the Coleoptera insect order, which includes beetles and weevils. Mealworms are larvae of *T. molitor* and normally infest stored grain. In addition, they are widely used as fishing bait. Numerous reports of occupational allergy have been attributed to members of the Coleoptera order (16–20). Bernstein et al. (21) evaluated 4 individuals with clinical sensitivity and positive skin tests to the larvae of *T. molitor*, and Schroekenstein et al. confirmed that beetles of the Tenebrionid family are potentially significant allergens for

workers exposed to grains or grain products (22).

Several studies performed during the last 10 years have strongly suggested that cockroach allergens are an important cause of asthma (23–31). These studies indicate that a high percentage of patients with asthma have significant skin test reactivity and serum IgE antibodies to cockroach allergens and can exhibit positive bronchoconstrictive responses on exposure to cockroach allergens included in stored food. These studies were performed with *Periplaneta americana* and *Blattella germanica*. In our area, the most important cockroach that infests stored grain is *B. orientalis*.

This article reports on clinical and immunological studies performed on 50 workers who developed allergic respiratory symptoms associated with exposure to emanations of stored grain pests.

MATERIAL AND METHODS

Analysis of Arthropod Fauna in Cereal Dust

We have analyzed the stored-grain pests fauna in cereal and flour dust to determine whether there is a clear relationship between environmental exposure to these pests and development of allergic symptoms. Ten dust samples were collected in April 1991. The samples came from 10 different storage areas (bakeries, farms, silos, stables) and were collected from dust on or near the floor and placed in clean plastic bags to search for beetles, cockroaches, and other arthropods. Samples with dry weights of 50 g were sieved (mesh size 1 mm) and treated by the Hart-Fain method (32).

Grain Pests Asthma

Live and dead mites were counted under a lens using a magnification of 400. Identification was performed in accordance with previous publications (8,33).

Preparation of *T. molitor* Extracts

For in vivo studies, 20 insects (10 larvae and 10 pupae) were frozen and then macerated in 10 ml of saline. Afterwards they were centrifuged for 2 min at 900 g and the supernatant was filtered through a sterilizing Millipore filter.

Serial dilutions were prepared to be used in prick test titration. Protein concentration of the extract was determined by the Lowry method (Bio-Rad Laboratories, Richmond, CA) with results of 8.9 mg/ml.

For in vitro studies the same number of mealworms were frozen, macerated, and defatted in acetone for 18 hr at room temperature and processed as previously described (18,21,22).

Selection of Patients

A population of 4379 persons residing in an area of cereal industries were evaluated in a clinical survey that included questionnaire, skin tests, and RAST studies, during a 3-year period.

Of these patients, 1395 were cereal workers and 2984 did not work with cereal. The questionnaire consisted of questions relating to rhinoconjunctivitis, coughing, wheezing and shortness of breath, allergic and occupational precipitants, contact with cereal, animal fodder, observation of insects in flour or cereals by the patient, length of exposure, and other epidemiological data.

Of these 4379 individuals, 791 (18.06%) presented prick and RAST positive to a mite (storage mites and house dust mites) or arthropod. Of these 791 patients, 94 were sensitized (prick and RAST positive) to a storage mite. Of the subjects sensitized to pests and with jobs related to cereal (bakers, farmers, pastry factory workers, producers of animal fodder, etc.), we selected 202 patients with daily contact with cereal and with sensitization to a grain pest. Of these 202 workers, only 50 workers agreed to be included in a more complete study with

challenge tests. All 50 patients suffered from nasal or pulmonary symptoms related to their occupational environment. Of these people, 26% were farmers, 29% bakers, 26% employed in manual labor (packing flour), and 19% were exposed to cereal when they stored cereal flours to feed their farm animals. Sixteen subjects were females and 34 males. Age ranged from 18 to 69 years, the mean age being 35.5 ± 13.4 years. The average time of exposure before the onset of the symptoms was 8.3 ± 2.9 years. Twenty-one patients were city dwellers and 29 came from rural areas. Twenty nonatopic and 20 atopic individuals (sensitized to grass pollen) without cereal dust exposure were employed as a control group.

All participants gave their consent and the procedure was approved by the local ethics committee.

All participants underwent the following tests.

In Vivo Tests

SKIN PRICK TESTS

Skin prick tests were performed with a standard panel of allergenic extracts, including putative occupational allergens in the participants under study, such as flours and their additives (wheat, barley, rye, oat, gluten, alpha gliadin, alpha-amylase, soybean lecithin), pollens (wheat, barley, rye, oat, and other cereals), molds (*Aspergillus fumigatus*, *Alternaria tenuis*, *Cladosporium herbarum*, *Ustilago* spp.), animal danders (dog, cat, horse, cow, rat, pig), mites (family Pyroglyphidae: *D. pteronyssinus* and *D. farinae*), subfamily Pyroglyphinae (*Euroglyphus maynei*), family Acaridae (*Tyrophagus putrescentiae*, *Acarus siro*), family Glycyphagidae (*Glycyphagus domesticus*, *Lepidoglyphus destructor*, *Blomia kulagini*, *Gohieria fusca*), family Chortoglyphidae (*Chortoglyphus arcuatus*). Extracts were supplied by Aristegui Laboratories (Bilbao, Spain). Concentration was 5000 E/ml. The extract of *B. orientalis* (concentration 1 mg/ml) was supplied by LETI Laboratories (Barcelona, Spain). Wheals were measured after 15 min; the wheal obtained was outlined by tracing on adhesive paper and then measured by planimetry (HAFF-planimeter 317). Reactions were meas-

ured in mm². Only wheals > 20 mm² were considered positive.

CONJUNCTIVAL PROVOCATION TESTS

These tests, with the same extracts used in aqueous form, were performed by using Hosen's technique (34) on those patients who had rhinoconjunctivitis.

BRONCHIAL CHALLENGE TESTS

These tests were performed on asthmatic patients, by the technique of Chai for common allergens. The challenge tests with mites, mealworm, and cockroach were performed using a technique previously described (5,35). The initial dose was a dilution that produced a 3-mm-diameter wheal by prick testing. Interpretation of results was carried out according to the standards of the American Thoracic Society (36).

Nonspecific bronchial reactivity tests with methacholine were carried out adopting the procedure and concentration proposed by Chatman et al. (37). We used a score system to define the degree of bronchial reactivity of 0 = no reactivity to 4 = very severe reactivity.

In Vitro Tests

Specific IgE to all allergens assayed in prick testing (pollens, flours, mites, *B. orientalis*, molds, and enzymes) was determined by CAP system (Pharmacia, Uppsala, Sweden), and the results were expressed in classes (0–4). Only classes > 2 were accepted as positive. Extracts from mealworm were coupled to cyanogen bromide-activated disks sheparose 4B (Pharmacia) at a concentration of 4 mg of protein per milliliter. Coupling efficiency was 88%. A direct RAST was performed with methods previously described (22). All assays were performed in duplicate. The average background count was subtracted from each result before data analysis.

Statistical Analysis

Groups were compared using the Mann-Whitney test for data on ratio-interval scale and chi-square test for data on an ordinal scale. The

level of significance was chosen to be 0.05 two-tailed.

RESULTS

Identification of Stored-Grain Pests

The degree of infestation varied from 420 to 10,000 mites/g dust (see Tables 2 and 3). *D. pteronyssinus* was the dominant species in these samples (50–88% of the total mite population). Within the Storage mite population, *L. destructor* was the dominant species ($\bar{x} = 42.35 \pm 32.96$, range 6–72%) followed by *D. farinae*, *Tyrophagus*, *Chorthoglyphus*, *Blomia*, *Glyciphagus*, and *A. siro*.

The most common arthropods (not mites) found in samples were the beetle *T. molitor* and its larvae (yellow mealworm) and the cockroach *B. orientalis* and its oothecas. Other arthropods observed in 2 samples were ants, and in one sample, the Coleopterus *Tribolium confusum*.

Prevalence of Sensitization to Stored-Grain Pests in the Patients

The prevalence of mite sensitization in the total sample studied (4379 patients) was 18.96%; standard error of the mean (SEM) 0.58, confidence index (CI) 95% 16.93–19.19). The prevalence of sensitization to storage mites among mite-sensitive patients was 11.88% (SEM 1.15, 95% CI 9.63–14.3). Among the 50 selected patients the most frequent sensitization, as shown by prick tests, RAST, and challenge tests, was to *D. pteronyssinus* (58%), followed by *D. farinae* (48%), *L. destructor* and *T. putrescentiae* (38%), *B. kulagini* (34%), and *A. siro* and *C. arcuatus* (24%). In addition to this, 22% of the patients presented negative prick and RAST for *Dermatophagoides* ssp. with positive test for storage mites.

Fifty percent of the 50 patients were sensitized to *T. molitor* (SEM 0.7, CI 95% 36–64), and 36% to *B. orientalis* (SEM 0.67, CI 95% 23–49) (see Table 3).

Other allergens causing sensitization were cereal flours (13 wheat flour and 3 barley dust), animal danders (8 cat, 1 dog), grass pollen and

Table 1. Results of Conjunctival, Bronchial, and Methacholine Challenge Tests

PA	CON	BRO	MET	PA	CON	BRO	MET
1	50	0	0	26	50	10	2
2	10	0	0	27	50	10	2
3	10	0	0	28	50	1	3
4	10	1	4	29	10	1	3
5	50	0	0	30	5	5	2
6	10	0.5	2	31	10	10	3
7	50	10	4	32	0	0	0
8	50	10	4	33	0	0	0
9	0	0	0	34	0	0	0
10	5	5	2	35	1	1	4
11	5	5	2	36	0	0	0
12	10	10	4	37	1	1	2
13	0	0	0	38	0	1	0
14	0.1	0.1	3	39	0	0	0
15	10	10	3	40	0.1	0.1	2
16	10	10	3	41	10	10	4
17	0	0	0	42	5	0.1	3
18	0	0	0	43	5	5	2
19	0.1	0.1	4	44	0	5	1
20	0	0	0	45	0	0	0
21	5	5	2	46	1	1	2
22	10	0	0	47	5	5	2
23	10	10	3	48	5	5	3
23	0.1	0.1	3	49	5	5	0
25	5	5	1	50	0	0	2
				χ	35.3	3	1.74
				σ	28.8	3.7	1.46

PA, patient; CON, conjunctival challenge (IU); BRO, bronchial challenge (IU); MET, methacholine tests.

Table 2. Levels of Infestation in Dust Samples

SAMPLE NUMBER	MITES/g	TENEbrio	B. ORIENTALIS	OTHER PESTS
1	680	2 mealworms	Fragments	—
2	8,500	Fragments	—	Ants
3	420	1 beetle	1 female	—
4	7,300	—	Fragments	—
5	4,600	—	Fragments	<i>Tribolium</i>
6	10,000	1 mealworm	—	—
7	1,400	Fragments	—	Ants
8	9,100	2 beetles	1 female	—
9	5,000	Fragments	Fragments	—
10	670	—	Oothecas	—

Table 3. Prevalence of Grain-Stored Pests

PARASITE	SIZE	PREVALENCE (%)	SE	CI 95%
<i>D. pteronyssinus</i>	50	58	0.069	44.4-71.6
<i>T. molitor</i>	50	50	0.070	36.2-63.8
<i>D. farinae</i>	50	48	0.070	34.2-61.8
<i>L. destructor</i>	50	38	0.069	34.6-51.4
<i>T. putrescentiae</i>	50	38	0.069	34.6-51.4
<i>B. orientalis</i>	50	36	0.068	22.7-49.3
<i>B. kulagini</i>	50	34	0.067	20.9-47.1
<i>A. siro</i>	50	24	0.060	12.2-35.8
<i>C. arquatus</i>	50	24	0.060	12.2-35.8
<i>G. domesticus</i>	50	18	0.060	9.2-16.4
<i>E. maynei</i>	50	12	0.047	6.9-20.3

SE, standard error; CI, confidence index.

legume dust (10 patients). (Ground dry legumes are used in our area as feed for cattle, and this legume dust can be parasitized). The farmers were the group of workers with most cosensitization to different allergens. No sensitization to cereal pests was found in the control nonatopic group and only an atopic patient presented sensitization to *B. orientalis*.

The association between positive prick tests and RAST sensitivity was good ($r = 0.8486$, $y = 0.67x + 0.66$) (Fig. 1). Thirty-two patients (64%) tested positively for methacholine, with a score of bronchial hyperreactivity of 1.7 (light-moderate) (Table 1). The most frequent pathologies observed were rhinitis-asthma (25 patients, 50%) followed by rhinoconjunctivitis (15 patients, 30%), asthma alone (6 patients, 12%), rhinitis alone (2 patients, 4%), and urticaria (2 patients, 4%). Asthma and rhinitis-asthma were more prevalent among farmers (77%), followed by flour packing workers (61.5%).

DISCUSSION

Sensitization to mites and stinging insects is a frequently reported cause of allergic disease (1-10). The role of insects in occupational allergy has been recorded, for the most part, as a series of isolated case histories in which the allergy was attributed to a variety of arthropods (16-22). It would seem important, therefore, to evaluate its prevalence in a larger series of patients and to study not only the distribu-

tion of arthropods and their relationship to clinical symptoms, but also the nature of their capacity as occupational allergens. This is the aim of the present study.

Workers occupationally exposed to grain dust have a high prevalence of respiratory symptoms (10,38). Grain dust contains biological contaminants, including mold spores, pollens, and insects (39-41). The most prominent components in cereal allergy are salt-soluble proteins, and recently several allergens associated with flour allergy have been purified (42,43). All of them belong to a single protein family, very important due to its potential role in grain protection from insect parasitization. They exhibit inhibitory activities against animal alpha-amylases and trypsin. Nevertheless, the pathogenesis of respiratory symptoms in grain workers and bakers remains obscure when sensitization to cereal flour cannot be proved.

Storage mites normally infest stored food and vegetable products, as well as grains (2-15). Several studies have shown that storage mites are the most important allergens in farming environments causing bronchial asthma and allergic rhinoconjunctivitis among farmers (1-3, 7,8,16-20). In Sweden, IgE-mediated allergy to storage mites is a far greater problem in the farming population and an important prevalence has also been shown among farmers in Scotland, Denmark, France, and Canada (2-4,9,44,45). Blainey and colleagues performed a survey in 133 grain-store workers and

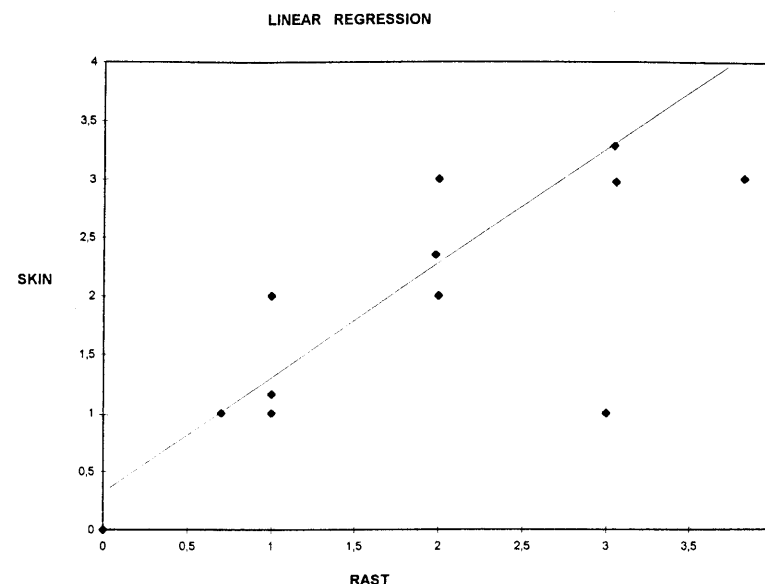


Figure 1. Association between positive prick tests and RAST sensitivity. We used a score system to define the area of wheals in skin tests: wheals < 20 mm² = 0; 20-30 mm² = 1; 30-40 mm² = 2; 40-50 mm² = 3; > 50 mm² = 4.

reported an association between occupational respiratory symptoms and positive skin tests and/or specific IgE to storage mites (10). Their study suggested that storage mites are an important cause of occupational respiratory symptoms in grain-store workers, a fact not recorded in previous surveys (46,47). Moreover, this pathology can also be frequent among bakers and in workers with other jobs related to grain processing (5,6,48). Recent publications based on the analysis of farm dust and clinical parameters have pointed out that *L. destructor* is the most important storage mite causing symptoms involving both upper and lower respiratory tract among farmers in Europe. Campbell et al. (49) have sampled barn air from barns in the United States and detected abundant *L. destructor*-derived aeroallergens. Our data regarding mite infestation in samples of cereal flour and clinical data are consistent with those of these authors. *L. destructor* and *T. putrescentiae* were the most important storage

mites causing symptoms in the patients included in our survey. Moreover, 22% of patients presented negative prick and RAST for *Dermatophagoides* with positive tests for storage mites. These results suggest that it is possible that individuals sensitized to storage mites do not improve after specific immunotherapy with *Dermatophagoides* extracts and raise the possibility that the need for hyposensitization has been underestimated (50).

T. molitor is an abundant stored-grain pest in the northern United States. Bernstein et al. demonstrated that inhaled particulates from *Tenebrio* exoskeletons are potent sensitizers and elicit IgE-mediated occupational asthma (21). Schroekenstein et al. (22) described a subject with occupational allergy to *T. molitor* and, by means of immunoblotting techniques, studied the allergens involved in this patient's immunological response. RAST inhibition showed immunological cross-reactivity between *T. molitor* and *Alphitobius diaperinus*, as

well as a slight cross-reactivity with blowfly. On the other hand, a barley flour inhibitor of *T. molitor* alpha amylase, is a major allergen associated with baker's asthma disease (51). We have found *T. molitor* and a small number of *Tribolium confusum* in the samples of cereal dust. Half of the 50 patients were sensitized to *T. molitor*. These results, together with the aforementioned studies, confirm that beetles of the Tenebrionidae family are potentially significant allergens for workers exposed to grains or grain products.

Cockroaches are an important source of allergens (23–31). Several studies indicate that a high percentage of patients with asthma have significant skin test reactivity and serum IgE antibodies to cockroach allergens. Nevertheless, there is the possibility that sensitization to cockroaches may be underestimated because of the limited number of German cockroach extracts currently marketed for skin testing. Lehrer et al. (28) demonstrated that commercial cockroach extracts vary in allergenic activity and that all house dust extracts tested contain cockroach allergens. On the other hand, the most important cockroach found in our samples was *B. orientalis*, and only *P. americana* and *B. germanica* have been extensively studied. Moreover, recently, Brenner et al. (52), working with American, German, and Oriental cockroach extracts, showed highly acidic bands in Oriental cockroach extracts that did not appear in extracts from American and German cockroaches. We found an important prevalence of sensitization to Oriental cockroaches, according to the level of infestation in dust samples.

Given the ubiquity of arthropods in stored vegetable products, it comes as a bit of a surprise that there are so few reports in the medical literature on allergy to arthropods as inhalants, compared to the many studies dedicated to other allergens. Reasons for the lack of interest in arthropod allergy would include the difficulty of collecting live arthropods for preparing extracts useful for diagnosis. The use of biologically standardized extracts of stored grain pests should improve the accuracy of prick testing allergic respiratory disease in grain workers. In fact, we found skin prick testing the most sensitive diagnostic criterion.

In conclusion, given the size of the cereal industry in the world, it is likely that large numbers of individuals are exposed to storage mites, mealworms, and cockroaches. Awareness of the potentially allergenic nature of these abundant stored-grain pests is of importance to the clinician, since such allergies may play a role in many cases of asthma usually attributed to grains in grain-dust asthma or baker's asthma.

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Asthma Training in Third-Year Medical Students

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ABSTRACT

To assess the educational experiences of physicians-in-training with asthma patients, we had medical students complete asthma surveys at the beginning and end of their internal medicine clerkship (IMC). At the beginning of the IMC, all students received a 1-hr asthma lecture and half of the students received a compilation of pocket cards containing many of the algorithms from the National Heart, Lung, and Blood Institute asthma guidelines. We found that students had relatively few encounters with asthmatic patients during the IMC. Students were good judges of asthma severity but performed poorly on survey questions pertaining to asthma treatment. Confidence in treating and assessing patients improved by the end of the IMC, but remained low. We conclude that the usual 1-hr lecture and limited contact with asthma patients during the IMC may be inadequate to train students to care for patients with asthma.

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