

Atopy and Systemic Reactions to Hymenoptera Stings

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ABSTRACT

To evaluate whether atopy is a risk factor for systemic reactions to hymenoptera stings, we compared the atopic status of two groups of subjects. The first group included 93 patients (59 males), mean ($\pm$ SD) age: 42.3 ± 17.2 yrs with a history of anaphylactic reactions to hymenoptera stings. The second was a control group of 712 subjects (379 males), mean ($\pm$ SD) age: 42.0 ± 9.6 years recruited at a public health care center. The protocol included a standardized questionnaire about symptoms suggestive of atopy, i.e. medical diagnosis of asthma, perennial rhinitis or hay fever, and skin tests to common aeroallergens, i.e. house dust mites, cat danders, and grass pollens. The percentage of subjects with atopic symptoms was comparable in the two groups (32.2% for the patient group and 28.5% for the control group). Similarly, 22.6% of patients and 36.8% of controls exhibited at least one positive skin prick test. Lastly, 15.1% of patients and 18.5% of controls (a non-significant difference) had at least one symptom of atopy and at least one positive skin test. These findings show that atopy is not a risk factor for systemic reactions to hymenoptera stings. (Allergy Proc 15:49–52, 1994)

Systemic reactions (SR) to hymenoptera stings (HS) are commonly present in up to 6.6% of the general population according to a recent report by our group¹ using medical history and skin tests to venoms as criteria. Since these SR are IgE-mediated, atopy is widely considered as a possible risk factor. In previous attempts to establish a connection between atopy and

SR to HS, atopy has mostly been defined on clinical grounds, i.e. history of symptoms of asthma, hay fever, perennial rhinitis, or childhood dermatitis. Although suggestive of atopy, the presence of these symptoms is not necessarily linked to specific IgE against common aero-allergens.² In this study, we compared the distribution of symptoms of atopy and skin tests to common aeroallergens in a group of 93 subjects with a history of SR to HS and a large control group.

SUBJECTS

Patient Group

The criterion for inclusion was a positive skin test to hymenoptera venom in patients referred to our department for SR to HS. Over a 1-year period, 93 patients were included (59 males, 34 females ranging in age from 26 to 60, mean ($\pm$ SD) age 42.3 ± 17.2 years).

Control Group

The control group consisted of 712 adults, 20 to 60 years old, recruited during routine medical examinations at the public health care center of the Bouches-du-Rhône district in Marseille. In France, all subjects affiliated with the Social Security System (i.e. 95% of the total population) have the opportunity to undergo a check-up every 5 years. We studied subjects visiting the center from January to July 1987. The group included 379 men and 333 women with a mean ($\pm$ SD) age of 42.0 ± 9.6 years.

METHODS

Questionnaire

For each patient and control, a short questionnaire was completed by an allergologist. The questions

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were designed to assess clinical atopy on the basis of clinical symptoms, i.e. hay fever, asthma, childhood dermatitis, and family history of atopic diseases.

Skin Tests to Hymenoptera Venom

Skin testing to hymenoptera venoms was performed using Honey bee, Yellow jacket, and Wasp venoms (Dome Hollister Stier Laboratories, Paris, France). Intracutaneous skin tests and point titration with serial 10-fold dilutions were started at 0.001 $\mu\text{g/ml}$. The dose was increased at 15-minute intervals until a positive reaction defined as a wheal and flare larger than 9 and 20 mm in diameter, respectively, was obtained. The maximum venom concentration was 1 $\mu\text{g/ml}$ since non-specific sting reactions can occur at concentrations of 10 $\mu\text{g/ml}$ or more. The solvent (saline) and codeine phosphate were used as negative and positive controls, respectively.

Skin Test to Common Allergens

Skin testing to common allergens was performed on the volar surface of the forearm by the prick test technique using the following allergens (Stallergenes Laboratories, Paris, France): Dermatophagoides farinae, Dermatophagoides pteronyssinus, cat danders, grass pollen. Such a limited number of allergens has been shown to efficiently demonstrate atopic background.³ Reactions were evaluated after 20 minutes and were considered positive if the diameter of the wheal was at least equal to half of the diameter induced by codeine phosphate.

Statistical Analysis

We compared the prevalence of atopic symptoms and percentage of positive skin tests in patients and control groups using a chi square test. The degree of statistical significance was chosen at 0.05.

RESULTS

Both the patient and control groups were made up mainly of middle-aged males. As shown in Table 1, the two groups did not differ significantly with respect to cumulative prevalence of each atopic symptom. The

TABLE I

	Patients n = 93	Controls n = 712
Asthma (%)	5.3	5.7
Perennial Rhinitis (%)	18.3	26.4
Hay Fever (%)	19.3	16.4
At least one symptom (%)	32.2	28.5

Prevalence of symptoms suggestive of atopy in the two groups.

TABLE II

	Patients	Controls
Dermatophagoides pteronyssinus and farinae	15.0%	29.8%
Cat danders	2.1%	6.3%
Grass pollens	11.8%	19.2%
At least one positive skin test	22.6%	36.8%

Percentage of positive skin tests in the two groups.

percentage of subjects complaining of asthma, perennial rhinitis, or hay fever was 32.2% in the patient group and 28.5% in the control group. As shown in Table 2, the two groups were also comparable with regard to distribution of positive skin tests. There was a nonstatistically significant trend for fewer positive skin tests in the patients' group. Seventy-seven % of patients and 63% of controls had negative skin tests. The percentage of patients with more than one positive skin test was also comparable.

Table 3 shows that the prevalence of atopy defined on clinical grounds, i.e. asthma, hay fever, perennial rhinitis, childhood dermatitis, and positive skin tests was similar in the two groups. In 15.5% of patients and 18.5% of controls, at least one symptom suggestive of atopy as well as one positive skin test to common aeroallergens was recorded (a non-significant difference).

DISCUSSION

This study demonstrates that atopy is not more common in patients with a history of SR to hymenoptera stings than in a control group. This holds true whether atopy is defined on a questionnaire or on skin test reactions to common aeroallergens. In our study groups, as in Golden's study,⁴ there was some sex-ratio imbalance, with more males in the patients' group. However, because skin test reactivity to common aeroallergens is known to be more common in males,^{2,4,5} this imbalance could only result in an overestimation of skin test reactivity in the patients' group. Thus, it

TABLE III

	Patients n = 14	Controls n = 132
At least one symptom suggestive of atopy +		
At least one positive skin test	(15.1%)	(18.5%)

Prevalence of atopy defined on the basis of symptoms and skin tests.

does not represent a bias in a study which did not show a higher percentage of skin test reactivity in the patients' group.

Several authors have attempted to determine whether HS allergy is related to atopic status. Most of them have defined atopy according to symptoms. Lockey et al.,⁶ in a population of 2181 sting-allergic subjects, reported 29.5% of atopic subjects. These authors defined atopy on the basis of clinical symptoms: asthma, allergic rhinitis, and atopic eczema. This percentage is in agreement with our data. Settipleane⁷ reported that the prevalence of atopy among patients with insect sting allergy was 13%, while Schwartz⁸ reported 63%. This large discrepancy seems to be primarily due to differences in methodology. Settipleane based his findings on responses of parents of 2964 boy scouts, 11 to 16 years old, to a questionnaire administered prior to a summer camp concerning bee or insect sting allergy and history of asthma and hay fever. Subjects did not undergo skin testing with any allergens, including insect extracts. The frequency of bee sting allergy in the 318 scouts with asthma and/or hay fever was 0.9% as compared with 0.8% in the 2639 scouts without asthma or hay fever, a difference which was not statistically significant. The prevalence of atopy was equal to 11% in the total population and 13% in the hymenoptera allergic population. In his study,⁸ Schwartz divided on the basis of clinical history 52 patients with hymenoptera sensitivity into two groups, 41 with systemic reactions and 11 with local hypersensitivity. The incidence of atopy was determined by carefully assessing the patient's history. Individuals who had a past history or a family history of asthma, hay fever, or atopic eczema were considered as atopic as were those who had no history but had positive skin tests to inhaled allergens (grass, tree, ragweed, fungal, animal danders, and house dust) or food (wheat, milk, egg, peanut, and salmon). Hypersensitivity to drugs was not considered to be evidence of atopy. Of the 41 patients with systemic hypersensitivity to hymenoptera, 14 were judged non-atopic. The prevalence of atopy in this HS allergic population (41 patients) was 63%. Przybilla et al.⁹ studied a large group of 525 patients with HS allergy in regard to atopic criteria. They demonstrated a history of atopic disease in 25%, a total serum IgE ≥ 100 KU/l in 48%, and at least one positive skin test to common aero-allergens in 53%. Unfortunately, there was no control group in this study. Besides, the authors suggested that, in the presence of at least one positive reaction to common aeroallergens, the threshold for skin tests to venom was lower.

Apart from our study, only one other investigation has used both symptoms and skin tests to common allergens to define atopy.³ This study has included a sample of 269 subjects from Westinghouse Electric Corporation. Subjects were asked about their histories

of previous stings and possible allergic reactions, as well as personal allergic history. Skin tests using a panel of common inhalant allergens were performed. The percentage of positive skin tests was 56% in subjects with a history of systemic reaction to HS, whereas it was 25% in subjects without such a history. Although this difference was statistically significant, it should be stressed that it is based on a small study group (nine subjects had a history of systemic reaction to HS).

Discrepancies between our findings and reports from the literature may be partly explained by criteria used to define atopy. In a previous epidemiological study performed in a health care center,² we have shown that the predictive value of questions related to asthma, perennial rhinitis, and even hay fever is low (less than 40% for the latter); the mean age of the study population is high. Thus, one would have to use skin tests to common inhalant allergens in order to properly identify atopy (alternatively RAST, which is a more expensive and less sensitive tool).

In contrast, atopy seems to be a predisposing factor for anaphylaxis in bee keepers. Bousquet¹⁰ evaluated atopy in a population of 250 bee keepers by means of a questionnaire and found that the percentage of bee keepers with a personal history of atopy was significantly higher among those who had anaphylactic symptoms than in those who had no anaphylaxis (41% vs 16%, $p < 0.02$). This is in agreement with other findings. Miyachi¹¹ reported an atopic background in 47% of allergic bee keepers (16/24 subjects) as compared with 13% of controls (6/47 subjects). Mueller¹² observed that the mean age at which HS allergy first becomes manifest was significantly lower among atopics (35.6% between 1 and 10 years old) than non-atopics (22% between 20 and 30 years old). The severity of the first anaphylactic reaction, especially in respiratory symptoms, was significantly greater in atopics than non-atopics. These observations suggest that atopy can influence the severity of clinical manifestations.

CONCLUSION

In conclusion, this study shows that the percentage of atopic subjects, defined by clinical symptoms and positive skin tests to common aero-allergens, was not higher in patients with a history of anaphylactic reaction to HS than in controls with no such history. This suggests that atopy is not a risk factor for the occurrence of anaphylactic reaction to HS, at least among non-bee keepers.

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BRIEF SUMMARY

CONTRAINDICATIONS: Azmacort Oral Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
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WARNINGS: Particular care is needed in patients who are transferred from systemically active corticosteroids to Azmacort Oral Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosolized steroids in recommended doses. After withdrawal from systemic corticosteroids, a number of months is usually required for recovery of hypothalamic-pituitary-adrenal (HPA) function. For some patients who have received large doses of oral steroids for long periods of time before therapy with Azmacort Oral Inhaler is initiated, recovery may be delayed for one year or longer. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis or other conditions with acute electrolyte loss. Although Azmacort Oral Inhaler may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies only normal physiological amounts of corticosteroid systemically and does NOT provide the increased systemic steroid which is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been recently withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Localized infections with *Candida albicans* have occurred infrequently in the mouth and pharynx. These areas should be examined by the treating physician at each patient visit. The percentage of positive mouth and throat cultures for *Candida albicans* did not change during a year of continuous therapy. The incidence of clinically apparent infection is low (2.5%). These infections may disappear spontaneously or may require treatment with appropriate antifungal therapy or discontinuance of treatment with Azmacort Oral Inhaler.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Azmacort Oral Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm. Patients should be instructed to contact their physician immediately when episodes of asthma which are not responsive to bronchodilators occur during the course of treatment with Azmacort Oral Inhaler. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by the administration of Azmacort Oral Inhaler in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone.

The use of Azmacort Oral Inhaler with alternate-day systemic prednisone could increase the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, Azmacort Oral Inhaler should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

Transfer of patients from systemic steroid therapy to Azmacort Oral Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS: During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION for details). Although steroid withdrawal effects are usually transient and not severe, severe and even fatal exacerbation of asthma can occur if the previous daily oral corticosteroid requirement had significantly exceeded 10 mg/day of prednisone or equivalent.

In responsive patients, inhaled corticosteroids will often permit control of asthmatic symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since triamcinolone acetonide is absorbed into the circulation and can be systemically active, the beneficial effects of Azmacort Oral Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Suppression of HPA function has been reported in volunteers who received 4000 mcg daily of triamcinolone acetonide. In addition, suppression of HPA function has been reported in some patients who have received recommended doses for as little as 6 to 12 weeks. Since the response of HPA function to inhaled corticosteroids is highly individualized, the physician should consider this information when treating patients.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects including suppression of growth in children. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of a decrease in adrenal function.

The long-term effects of triamcinolone acetonide inhaler in human subjects are not completely known, although patients have received Azmacort Oral Inhaler on a continuous basis for periods of two years or longer. While there has been no clinical evidence of adverse experiences, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea and lung are also unknown.

Azmacort Oral Inhaler should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex. The potential effects of long-term administration of Azmacort Oral Inhaler on lung or other tissues are unknown. However, pulmonary infiltrates with eosinophilia have occurred in patients receiving other inhaled corticosteroids. When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Azmacort Oral Inhaler should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Carcinogenesis, Mutagenesis: Animal studies of triamcinolone acetonide to test its carcinogenic potential are underway.

Impairment of Fertility: Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m²/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 22.9 mcg/kg/day (889 mcg/m²/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m²/day or 110 mcg/m²/day, respectively, as calculated on a surface area basis) exhibited dysplasia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5-15.0 mcg/kg/day or 20-110 mcg/m²/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and non-toxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m²/day and 7.0 mcg/m²/day).

Pregnancy: Pregnancy Category C. Like other corticosteroids, triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects, which occurred in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m²/day in the rat and 320, 640 and 1280 mcg/m²/day in the rabbit, as calculated on a surface area basis), included a low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformations, have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mcg/m²/day). Administration of aerosol by inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes. There are no adequate and well-controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need corticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Azmacort Oral Inhaler is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in children below the age of 6. Oral corticosteroids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS: A few cases of oral candidiasis have been reported (see WARNINGS). In addition, some patients receiving Azmacort Oral Inhaler have experienced hoarseness, dry throat, irritated throat and dry mouth. Increased wheezing and cough have been reported infrequently as has facial edema. These adverse effects have generally been mild and transient.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Please see product circular for full prescribing information.

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