

Anaphylactic reactions to Hymenoptera stings in asthmatic patients*

G. A. SETTIPANE, F. H. CHAFEE, D. E. KLEIN, G. K. BOYD,
J. H. STURAM and H. B. FREYE

Program in Medicine, Brown University and the Division of Allergy, Departments of Medicine and Pediatrics, Rhode Island Hospital, Providence, Rhode Island, U.S.A.

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Summary

We evaluated 587 cases with generalized reactions to stings of Hymenoptera. Eighty of these patients and twenty-eight normal controls had radioallergosorbent tests (RAST) to venoms of honey bee, yellow jacket, hornet, wasp and to phospholipase A. Those patients with systemic reactions had a significantly greater frequency of positive RAST than normal controls (51.3% *vs.* 7.1%, $P < 0.001$). The frequency of atopy (asthma/rhinitis) in these 587 cases was only 22% and resembled the expected frequency in a general population. Asthmatic patients did not have an increased risk of developing systemic reactions to Hymenoptera stings. However, those asthmatic patients with systemic reactions to Hymenoptera stings had a significantly more severe anaphylactic reaction to a sting than non-asthmatics. These severe reactions were primarily manifested by acute dyspnoea, which appeared to represent a bronchospastic response to endogenous histamine release.

Introduction

Our past investigations (Settipane, Klein & Boyd, 1978; Settipane, Newstead & Boyd, 1972) demonstrated that atopy (asthma/allergic rhinitis) does not predispose one to other acute anaphylactic reactions such as generalized allergic reactions to Hymenoptera sting. However, one of our recent studies (Settipane *et al.*, 1978) revealed that asthmatic patients who also have a generalized reaction to Hymenoptera sting appear to have a more severe anaphylactic reaction to the sting than non-asthmatic individuals. The present investigation was undertaken to enlarge our population sample in order to determine if we could confirm and add to our previous findings.

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Materials and methods

Patients with a generalized allergic reaction to Hymenoptera stings (wasp, yellow jacket, hornet and honey bee) in the Rhode Island Allergy Clinic and in our private practices were evaluated. An allergic reaction to Hymenoptera sting is defined as generalized hives/angioedema (grade II), acute dyspnoea (grade III), or a degree of syncope (grade IV), occurring shortly after the sting. Patients with local reactions regardless of size (grade I), were not included in this study. Toxic reactions due to multiple stings were also excluded.

There were 587 patients with generalized reactions to Hymenoptera sting. Information from 192 of these patients was obtained from direct personal interviews and data from 119 of these patients have been reported (Settippane *et al.*, 1978). Information from other patients was obtained from consecutive office and clinic records. When charts were incomplete, an attempt was made to contact these patients. If pertinent information was still not available, these cases were not included in our study. All questionable cases of allergy to Hymenoptera sting were also excluded.

In eighty patients with allergy to Hymenoptera stings and in twenty-eight normal controls without generalized or large local reactions to stings, blood was drawn and sera were frozen and stored. These sera were later sent in a frozen state to private laboratories* for specific IgE determinations to venoms of the honey bee, yellow jacket, hornet, wasp and to phospholipase A. These tests were done in duplicate and results were averaged. The laboratories were not told which sera belonged to the normal controls. These laboratories described the antigens as follows. Honey bee venom was obtained from live insects by an electric shock method. Phospholipase A, Grade I, was purchased from Sigma Chemical Company, St. Louis, Missouri. Yellow jacket, hornet and wasp venoms were obtained from dissected venom sacs which were crushed in a B-alanine/acetic acid buffer to release venom. The sac residue were then removed by filtration and centrifugation. Venoms were stored in a tris-saline buffer, pH 7.35, containing 0.03% human serum albumin. The collection and identification of insects and the analysis of venom proteins were monitored by Allen W. Benton, Ph.D., Professor of Entomology, Pennsylvania State University.

A diagnosis of asthma was accepted if symptoms consisted of clinically reversible signs of wheezing, shortness of breath and cough on a recurrent basis, not due to any other disease. A diagnosis of rhinitis was accepted if symptoms consisted of recurrent nasal stuffiness, rhinorrhea and frequent sneezing on a seasonal or non-seasonal basis. Cases of infectious rhinitis were excluded. Those patients with both asthma and rhinitis were classified as asthma and only those patients with rhinitis alone were classified as rhinitis. For this study, atopy is defined as having a past or present history of asthma or rhinitis.

Results

Of the total 587 patients with generalized reactions to Hymenoptera sting, 416 (71%) were males and 171 (29%) were females. Fifty percent were aged 12 years or less at the time of the initial systemic reaction to Hymenoptera. Of the 587 patients, fifty-six (9.5%) had a history of asthma, seventy-five (12.8%) had a history of recurrent rhinitis and 456 (77.7%) were classified as non-atopic patients (no history of asthma/rhinitis) (Table 1).

* Pharmacia Diagnostics, Piscataway, New Jersey, Genatom, East Orange, New Jersey, and Aid Service Corporation, Princeton, New Jersey.

Table 1. 587 systemic reactions to Hymenoptera: characteristics of population

Clinical data	Number	Percentage
Males	416	70.9
Females	171	29.1
Age 12 or younger	295	50.2
Asthma	56	9.5
Rhinitis (alone)	75	12.8
Non atopic	456	77.7

Only 10.2% of our total (587) patients did not have an associated generalized hives/angioedema with their anaphylactic reaction to Hymenoptera stings. The frequency of asthmatic patients with grade III/IV reactions without generalized hives/angioedema was not significantly different from non-atopic and rhinitis patients in a similar category (Table 2). A large number of our grade IV reactions (syncope) also had an associated dyspnoea.

Asthmatic patients had a significantly more severe reaction (grade III/IV) to the sting than non-atopic patients, 69.6% *vs* 43.6% ($P < 0.001$). These asthmatic patients did not differ significantly in grade IV reactions (syncope) from non-atopic (25.0% *vs* 20.8%) and rhinitis patients (25.0% *vs* 32.0%) (Table 3). The main difference was in grade III reactions (dyspnoea) where the asthmatic patients had a significantly greater frequency than non-atopic patients, 44.6% *vs* 22.8% ($P < 0.001$) and than rhinitis patients, 44.6% *vs* 22.7% ($P < 0.01$).

When those patients with grade IV reactions and dyspnoea were added to the grade III reactors, 60.7% of the asthmatic patients experienced dyspnoea with their anaphylactic reaction to Hymenoptera sting and this was significantly greater than non-atopic, 30.5% ($P < 0.01$) and rhinitis patients, 36.0% ($P < 0.01$) (Table 3). Similarly patients of 12 years of age or younger with asthma, rhinitis or non-atopics resembled the over-12 age group with respect to their reactions.

Table 2. 587 allergic reactions to Hymenoptera: grade III/IV reactions without hives/angioedema

Diagnosis	Grade III/IV reactions			
	Total	No. without hives/angioedema	Percentage	<i>P</i> value
Asthma	39	10	25.6	n.s.
Non-atopic patients	199	42	21.1	
Rhinitis (alone)	41	8	19.5†	n.s.
Total	279	60	21.5	

† 19.5% *vs* 25.6% is not statistically significant (n.s.).

10.2% (60/587) of total population had no associated hives/angioedema.

Table 3. 587 systemic reactions to Hymenoptera: total population

Diagnosis	Total	Grade of reactions								
		IV				III				Dyspnoea
		No.	Percentage	<i>P</i> value	No.	Percentage	<i>P</i> value	No.	Percentage	<i>P</i> value
Asthma	56	14	25.0	n.s. <0.05	25	44.6	<0.001 n.s.	34	60.7	<0.001 n.s.
Non atopic	456	95	20.8		104	22.8		139	30.5	
Rhinitis	75	24	32.0		17	22.7		27	36.0	
Total	587	133	22.7		146	24.9		200	34.1	

The difference between asthma and rhinitis is significant in the grade III reactors (44.6% vs 22.7%, $P < 0.01$) and in the dyspnoea group (60.7% vs 36.0%, $P < 0.01$)

Table 4. Positive RASTs to venoms of wasp, yellow jacket, hornet, honey bee and phospholipase A

Population	Total	One or more positive	Percentage	<i>P</i> value
Generalized allergic reaction to hymenoptera	80	41	51.3	<0.001
Normal controls	28	2	7.1	

In the prospective portion of our study, we found no relationship between asthmatic patients with positive skin tests to pollens, danders or moulds and the severity of reaction to Hymenoptera. Eighty percent of our asthmatic patients in this part of our study required medication for control of their asthma within 2 years of the sting that caused the anaphylactic reaction.

Of the eighty sera from patients with allergy to Hymenoptera, 51.3% had one or more positive RAST for specific IgE to venoms of honey bee, yellow jacket, hornet, wasp and to phospholipase A, while only two out of twenty-eight normal control patients (7.1%) had one or more positive RAST to these antigens. This difference is statistically significant (51.3% vs 7.1%, $P < 0.001$) (Table 4). Asthmatic patients did not have a significantly greater frequency of positive RAST, 22.2%, (2/9), compared to non-atopic patients, 56.3% (36/64), or rhinitis patients, 42.9% (3/7). Asthmatic patients also did not have a significantly higher titre of positive RAST than other patients.

Discussion

The predominance of males (71%) in our population appears to be a social and environmental artifact. Since males are outdoors more than females, they have increased exposure and thus an increased risk of developing allergic reactions to Hymenoptera stings. In a population of girl scouts and boy scouts of similar age and similar outdoor habits, the frequency of allergy to Hymenoptera stings was similar (Settipane & Boyd, 1970; Abrishami, Boyd & Settupane, 1971).

Most of our 587 patients with allergy to Hymenoptera stings were not atopic for

only 22% had a history of asthma or rhinitis. In fact, the frequency of atopy (asthma/rhinitis) in these 587 patients is similar to that found in a normal population (Hagy & Settupane, 1969, 1971, 1976; Settupane *et al.*, 1978). In our previous investigation, we examined 119 patients with generalized reactions to Hymenoptera stings by determining the total serum IgE, response to allergy skin tests to pollens, danders and moulds, and the personal and family history of asthma and rhinitis. We found that a great majority of these patients were non-atopic when examined by these immunological and clinical procedures. It appears, therefore, that atopy (asthma/rhinitis) does not predispose one to other acute anaphylactic sensitization.

RAST for specific IgE to venoms of honey bee, wasp, yellow jacket, hornet and to phospholipase A appear to differentiate a population with generalized reactions from normal controls (51.3% *vs* 7.1%, $P \leq 0.001$) (Table 4). However, false negative and false positive RAST to venoms have been reported (Müller, Speiss & Roth, 1977). False negative reactions may be due to the time interval between the generalized reaction to a sting and the time when blood was drawn. Blood drawn within 2 weeks (anergic period) and over 5 years after the generalized reaction may result in negative RAST (Reisman & Arbesman, 1975; Findlay *et al.*, 1977; Settupane & Chafee, 1979). In addition, those normal patients with positive RAST to venoms may be at high risk for future generalized reactions.

Although asthmatic patients do not have an increased risk of developing generalized allergic reactions to Hymenoptera stings, they have a significantly higher risk than others of developing severe reactions. This severe reaction is manifested by acute dyspnoea which does not appear to be related to an increased frequency or increased titre of positive RAST to venoms.

It is possible that asthmatic patients may have increased anxiety to a sting causing them to have a higher frequency of acute dyspnoea than other patients. However, the asthmatic patients with grade III/IV reactions have a similar frequency of generalized hives/angioedema associated with their reaction as other patients. Since acute urticaria/angioedema is our strongest evidence for an acute anaphylactic reaction, it appears unlikely that the asthmatic patient's increased frequency of severe reactions is related to a higher degree of anxiety. The probable mechanism of dyspnoea (acute bronchospastic reaction) found in asthmatic patients with anaphylaxis may be related to an increased sensitivity to histamine. A review of the literature appears to support this hypothesis.

Histamine release occurs when venoms of Hymenoptera used as antigens are mixed *in vitro* with leucocytes from patients with a history of generalized reactions to Hymenoptera sting (Yocum, Johnston & Condemi, 1973; Sobotka *et al.*, 1974). Other investigators (Weiss, Robb & Blumgart, 1929; Curry, 1946) have reported that asthmatic patients respond with acute bronchospasm when histamine is administered intravenously. Non-asthmatic patients usually do not have bronchospasm with intravenous histamine. When challenged with an aerosolized antigen to which they are sensitive, asthmatic patients respond with acute bronchospasm and an increase in plasma histamine level (Bhat *et al.*, 1976). The association between histamine and asthma was noted again by Simon *et al.* (1977). They demonstrated that plasma histamine level was increased in patients with severe asthma compared to asthmatic patients in remission, as well as non-asthmatic controls. In a recent report (Brown *et al.* 1977), it was stated that asthmatic patients with an initial abnormal pulmonary function test appeared to have relatively more bronchospasm with intravenously

administered histamine. Our data indirectly supports this conclusion for 80% of the asthmatic patients in this study were considered to have active disease, in that they had required medication for the control of their asthma within 2 years of the sting that had caused an anaphylactic reaction.

Other mediators of anaphylaxis, such as slow-reactive substance of anaphylaxis, (SRS-A), kinins, eosinophilic chemotactic factor of anaphylaxis (ECF-A), and prostaglandins may also be important mediators of acute bronchospasm associated with anaphylaxis, but their role had not been as clearly delineated as the role of histamine. It is probable that asthmatic patients do not have an increased risk of developing acute sensitization to other antigens such as penicillin. However, after a sensitivity occurs, they may respond to the next antigenic challenge with an additional symptom of acute bronchospasm.

In summary, atopy (asthma/rhinitis) does not appear to predispose one to acute anaphylactic sensitization. However, when an anaphylactic reaction does occur, asthmatic patients experience an additional symptom of acute bronchospasm which is probably secondary to an increased pulmonary sensitivity to histamine release.

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