

The seasonal symptoms of hyposensitized and untreated hay fever patients in relation to birch pollen counts: correlations with nasal sensitivity, prick tests and RAST

M. VIANDER and A. KOIVIKKO

*Departments of Medical Microbiology and Pediatrics,
University of Turku, Turku, Finland*

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Summary

A 2 year prospective study of thirty-eight birch pollen-sensitive hay fever patients under specific immunotherapy and of nineteen untreated control patients showed a significant correlation between the total seasonal symptom scores of the patients and their clinical sensitivities assessed by the RAST and a graded nasal test. The agreement between a positive nasal test and a positive RAST was 74%. In the early season with low pollen counts the onset of symptoms was significantly associated with high sensitivity of the patients, while many patients showed symptoms in the late season irrespective of their nasal and RAST sensitivity. About 90% of both the treated and the untreated patients reported mild symptoms when the pollen count exceeded 80/m³ in the early season. 80% of them still had symptoms when the count was below 30/m³ in the late pollen season. Although hyposensitization therapy had no effect on the occurrence of the mild symptoms, the treated patients had severe symptoms significantly less often than the untreated ones on days with high pollen counts.

Introduction

The importance of a quantitative pollen count in obtaining the clinical history of the patients and in the evaluation of the treatment of respiratory allergic diseases has been emphasized (Norman, 1969; Davies, 1975). A good correlation between the symptoms of the patients and the pollen counts has been found in a number of studies (Sack & Golan, 1942; Lowell & Franklin, 1963; Brown & Ipsen, 1968; Norman, Winkenwerder & Lichtenstein, 1968). However, there are few reports of the amount of pollen required to provoke symptoms in allergic subjects (Rackeman & Smith, 1931; Ogden & Lewis, 1960; Frankland & Davies, unpublished results, see Davies & Smith, 1973; Fuckerieder, 1976), and only some estimates of the dependence of the first seasonal symptoms of the patients on their clinical sensitivity and the pollen counts (Hyde, 1972).

Correspondence: Dr Markku Viander, Department of Medical Microbiology, University of Turku, SF-20520 Turku 52, Finland.

In most of the earlier reports subjects with grass or ragweed pollen allergy were studied. The high frequency of birch pollen allergy in the Scandinavian countries (Juhlin-Dannfelt, 1948, Björkstén & Johansson, 1975) and the characterization of the main allergens of birch pollen (Belin, 1972) both make the birch pollen-allergic subjects suitable for clinical and immunological studies. This report gives clinical and aerobiological data of a 2 year prospective study of the clinical and immunological findings in birch pollen-allergic hay fever patients under immunotherapy and their untreated controls.

Special interest was focused upon the amount of pollen required to precipitate symptoms in the treated and untreated subjects, and the dependence of their first seasonal symptoms on their clinical sensitivity, in terms of the RAST and a graded nasal test.

Materials and methods

Patients

A group of thirty-eight hay fever patients was selected for specific immunotherapy on the basis of symptoms of allergic rhinitis during birch pollen seasons. Diagnosis was confirmed by a positive prick test and a positive nasal provocation test with whole birch pollen extract. Some of the patients showed additional sensitivities. An age-matched control group of nineteen patients was selected in the same way. Details of the patients are shown in Table 1.

Birch pollen extract

The pollen preparations used in this study were all of the same origin: *Betula pendula* (*verrucosa*) lot 464, kindly provided by Dome Laboratories Ltd, England. The purity

Table 1. Comparability of hyposensitized and control groups

Patient details	Treated	Controls
Number of patients	38	19
Sex distribution		
Female	21	12
Male	17	7
Age (in years)		
Mean (range)	20.0 (5-46)	21.2 (6-42)
Duration of disease (in years)		
Mean (range)	4.8 (2-11)	5.4 (2-15)
Allergy		
Birch pollen only (<i>n</i>)	14	10
Birch plus grass pollen (<i>n</i>)	24	9
Respiratory symptoms		
Hay fever only (<i>n</i>)	32	15
Hay fever plus pollen asthma (<i>n</i>)	2	1
Hay fever plus perennial rhinitis (<i>n</i>)	4	4
Atopic eczema (<i>n</i>)	4	4

of the pollen was 99.8%, checked by microscopic examination at the Department of Botany, University of Turku.

Birch pollen extract was prepared by extraction of 1.0 g of non-defatted pollen in 10 ml of phosphate-buffered saline (equal parts of 0.15 M phosphate buffer, pH 7.2, and of physiological saline) by mild shaking at 4°C for 24 hr. The extraction was terminated by centrifugation at 22,000 g for 20 min and the supernatant was sterilized by a 0.45 µm millipore filter, and stored in small portions (1 : 10 w/v) at -20°C until used.

In vivo tests

Skin tests. To the extract used for skin tests 50% glycerol and 0.5% phenol were added. A 1.0% (w/v) extract was used for skin prick testing. The weal sizes were compared with that of a 0.1% histamine hydrochloride solution, according to the recommendations of the Standardization Committee of Northern Society of Allergy (Aas & Belin, 1972). Thus a weal reaction of the same size as that of the histamine reference was recorded as 3+ reaction, a weal size half of that as 2+ and weal size double the size of histamine reference as 4+. The weals a little greater than the buffer control were given 1+.

Nasal tests. Fresh test solutions of 5%, 1% and 0.1% were prepared every 3 weeks. The patients had to be symptom-free (verified by anterior rhinoscopy) and all therapy with antihistamines, steroids, sympatomimetics and methyl xanthine derivatives was stopped 72 hr before the *in vivo* testing. After instillation of 0.05 ml of the extract with a 1.0 ml disposable syringe into one side of the nose, the patient was asked to sniff. A control test was made with the dilution buffer on the opposite side. Tests with the birch pollen extract were made with increasing concentrations, starting with 0.1% (w/v) and proceeding, if negative, after intervals of 15 min, to tests with 1% and 5% concentrations. A positive reaction was recorded if the test provoked itching of the nose or eyes, rhinorrhoea, sneezing, swelling of the nasal mucosa and nasal obstruction.

RAST tests

Specific IgE against birch pollen was measured by a paper disk RAST (Phadebas®, Pharmacia, Uppsala, Sweden). Blood was taken at the time of the nasal testing, 4-6 months after the birch pollen season, and kept frozen at -20°C until the RAST determinations were made simultaneously. Duplicate measurements were carried out, according to the directions of the manufacturer. The RAST reference was run parallel with the samples, thus enabling classification of the results. RAST class 0 was regarded as negative and classes 1 to 4 as indicating the presence of circulating IgE antibodies in increasing concentrations. Class 1 was regarded as a borderline value.

Birch pollen counts

Quantitative daily pollen counts were based on the results of continuous collection with a Hirst-Burkard volumetric automatic spore trap in Turku (Hirst, 1952). The samples were analysed weekly and the results were subsequently published in the Finnish Pollen Bulletin by the Finnish Aerobiology Group in Turku (Department of Botany, University of Turku, SF-20500 Turku 50, Finland).

Treatment

All patients were treated with two series of pre-seasonal injections with a pyridine-

extracted alum-precipitated whole birch pollen extract (Allpyral®) prepared by Dome Laboratories from the same batch of *Betula pendula* pollen as mentioned above. Some of the patients were additionally treated with grass and alder pollen extracts. The dosage of the Allpyral birch extract was as follows: starting in the first year from 2.5 pnu (protein nitrogen unit) as an eleven dose schedule, and terminating in most patients with 2000–4000 pnu after the first and 4000–7000 pnu after the second year of treatment. In practice, the final doses given depended on the clinical sensitivity of the patients, e.g. eleven out of thirty-eight patients in the first year and four out of thirty-eight in the second year did not tolerate doses over 1000 pnu.

Clinical assessment

Symptom diary. The daily symptom diary was a modification of that previously described by Norman *et al.* (1968). The patients were asked to record separately the symptoms from their nose, eyes and chest. Furthermore, the duration of the symptoms and the need for antihistamine tablets (dexchlorpheniramin, by the courtesy of Essex Lääkkeet, Schering Corp., Helsinki) were asked.

The daily symptom score. This was the sum of the numerical values (0–3) given by the patients for each of the symptoms: (0) no symptoms, (1) mild symptoms, less than 2 hr, no need of medication, (2) moderate, 2–6 hr, relieved by medication, (3) severe symptoms, longer than 6 hr, not relieved by medication. In addition, the number of antihistamine tablets (0, 1 or 2) taken was added to the daily symptom score.

The total or cumulative symptom score. This was the sum of the daily symptom scores during the main birch pollen season, from May 5 to June 4, each year.

Statistical methods

Non-parametric tests were employed for the statistical analyses. The Fisher exact probability test was used to determine the relationship between the *in vivo* and *in vitro* tests. Scores were analysed by the Mann–Whitney U test, χ^2 test and the Spearman rank correlation coefficient (r_s).

Results

Comparison between nasal tests, skin tests and RAST

All these comparisons are based on tests performed before immunotherapy in both groups of patients.

Nasal tests. The distribution of the hyposensitized and control patients according to the nasal sensitivity and the RAST class is shown in Fig. 1. A significant association of a high (class 3–4) RAST with the highest nasal sensitivity (0.1% w/v extract) was found in both groups ($P < 0.002$ and $P < 0.05$, respectively). The agreement of a positive (class 2–4) RAST with a positive nasal test was 73.7% in both groups of patients.

Skin tests. The agreement of a positive 3+ or stronger prick skin test with a positive RAST was 78.7% and that of a 4+ prick test was 90%. There was a tendency towards a higher nasal sensitivity in patients with 3+ or 4+ prick reactions, but this was not statistically significant. A significant association of a 4+ prick reaction with a positive RAST was, however, found when both patient groups were combined ($P < 0.05$, Fig. 1).

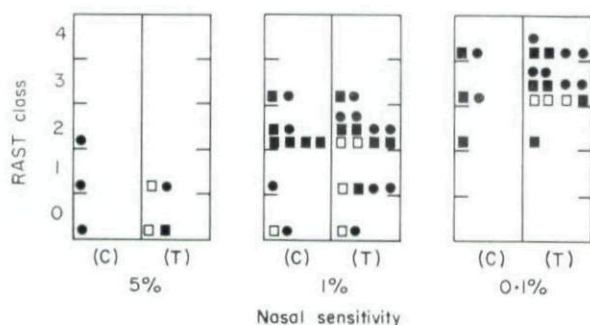


Fig. 1. Comparison between the results of nasal provocation tests, prick tests and RAST of treated (T) and control (C) patients. (□) Prick test 1+ or 2+; (●) prick test 3+; and (■) prick test 4+.

Correlation of RAST, prick and nasal tests with seasonal symptoms

The distribution of the hyposensitized and control patients according to the total seasonal symptom score, nasal sensitivity and RAST results in 1976 is shown in Fig. 2. Since no correlation was obtained between the skin sensitivity and the symptom score of the patients, these data are not shown.

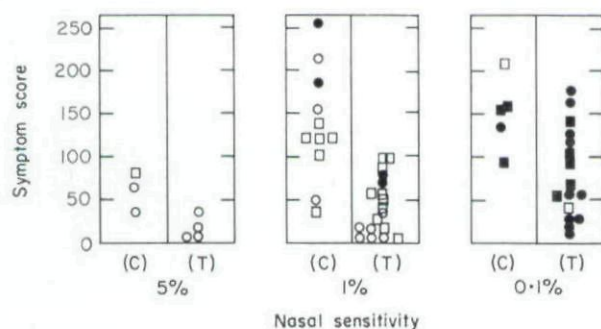


Fig. 2. Correlation of pre-treatment nasal tests and RAST results with seasonal symptoms in 1976. (T) Treated patients; (C) controls; (○) RAST class 0-1; (□) class 2; (●) class 3; and (■) class 4.

Nasal tests. There was a significant correlation between the nasal sensitivity and the seasonal symptom score of both the untreated and the treated subjects ($r_s = 0.68$, $P < 0.001$, and $r_s = 0.62$, $P < 0.001$, respectively). The symptoms of the treated patients were significantly milder than those of the untreated patients in each of the nasal sensitivity classes (5%, $P < 0.05$; 1%, $P < 0.002$; and 0.1%, $P < 0.01$).

RAST. There was a significant association between a positive (class 2-4) RAST and higher total symptom score in the untreated and treated patients ($P < 0.02$ and $P < 0.002$, respectively, Fig. 2).

Dependence of seasonal symptoms on pollen count

Mild symptoms (daily symptom score 2 or less). The proportion of hyposensitized and control patients with mild or severe symptoms in relation to the daily pollen

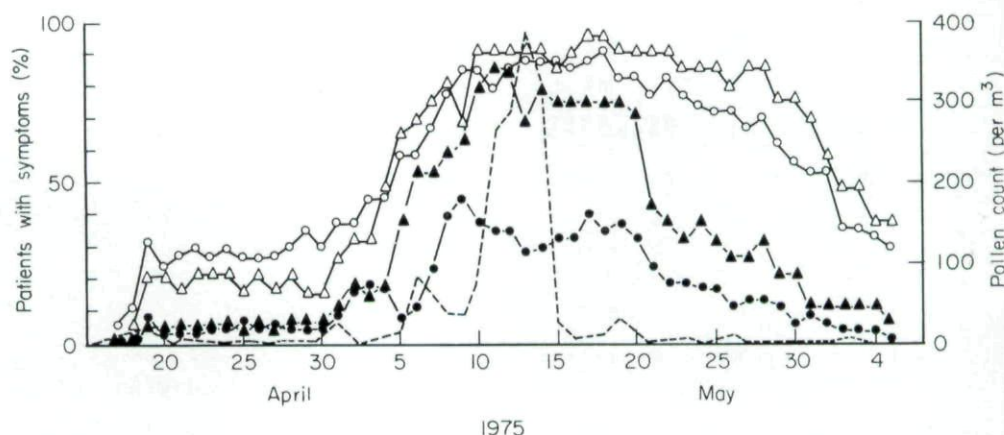


Fig. 3. Percentage of hyposensitized and control patients with symptoms in relation to the daily pollen counts in 1975. (○) and (△) All hyposensitized and control patients with symptoms; (●) and (▲) hyposensitized and control patients with severe symptoms (i.e. symptom score 3 or more); (---) daily birch pollen count.

counts in 1975 is seen in Fig. 3. No difference in the occurrence of the mild symptoms could be seen between the two groups. The appearance of the first symptoms was clearly dependent on the pollen count in the early season, and about 90% of all the patients had their first symptoms when the pollen count exceeded 80/m³ (Table 2).

Table 2. Dependence of the first seasonal symptoms on birch pollen count in 1975

Pollen count (per m ³)	Patients with symptoms (%)	
	Treated	Controls
10	13.1	15.8
20	36.8	57.9
30	52.6	73.7
80	86.8	89.5
250	100.0	100.0

The appearance of symptoms at pollen counts below 30/m³ in the early season was significantly associated with a high nasal sensitivity ($P < 0.05$) and a high RAST class in the patients ($P < 0.05$, Fig. 4). On the other hand, about 80% of all the patients, irrespective of their nasal or RAST sensitivity, still had symptoms when the pollen count was below 30/m³ for 2 weeks in the late season (Fig. 3).

Severe symptoms (daily symptom score 3 or more). The occurrence of severe symptoms coincided with the peak pollen season, i.e. daily pollen counts greater than 30/m³ (Fig. 3). The percentage of hyposensitized patients with severe symptoms during the peak pollen season was significantly lower ($\chi^2 = 6.63$, $P < 0.01$) than that of the untreated control patients. Furthermore, the untreated patients had severe symptoms

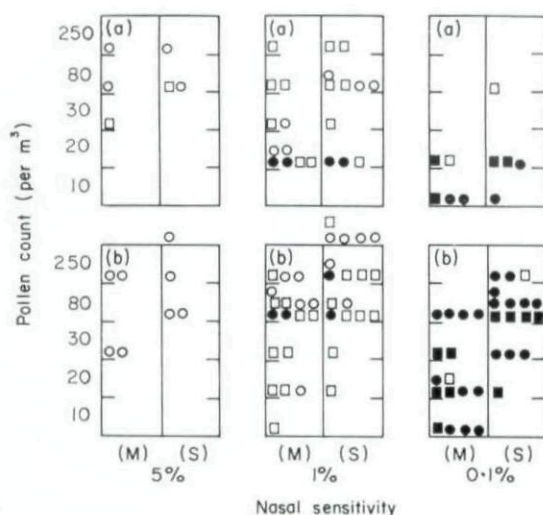


Fig. 4. Dependence of the occurrence of the first mild (M, symptom score 2 or less) or severe (S, symptom score 3 or more) symptoms in 1975 on nasal sensitivity, RAST class and birch pollen counts. (a) Controls; (b) treated patients; (○) RAST class 0-1; (□) class 2; (●) class 3; and (■) class 4. Open symbols at the top of two columns indicate treated patients with no severe symptoms.

Table 3. Dependence of the occurrence of severe symptoms on birch pollen count in 1975

Number of patients with severe symptoms	Pollen count (per m ³)				
	10	20	30	80	250
Treated	0	2	4	17	9
Controls	1	6	1	8	3

Fisher exact probability test, $P < 0.025$.

significantly more often than the treated ones when the pollen count was below 30/m³ in the early season ($P < 0.025$, Table 3). Accordingly, the appearance of severe symptoms at low pollen counts was significantly dependent on the clinical sensitivity of the untreated patients, determined by the RAST ($P < 0.001$) or by the nasal test ($P < 0.05$, Fig. 4). However, no correlation could be obtained between the onset of the severe symptoms and the sensitivity of the treated patients. In fact, six of the treated patients did not report having severe symptoms at all, even with pollen counts exceeding 250/m³.

Discussion

The aims of the present study were two-fold: to study precisely how a quantitative pollen count can predict the appearance of the first seasonal symptoms of birch pollen-allergic subjects, and what effect the clinical sensitivity of the untreated or hyposensitized patients has on this relationship.

The degree of clinical sensitivity was determined by nasal provocation tests and the

RAST. The agreement between a positive nasal test and a positive RAST was 74%, which is of the same order as found in some studies of pollen allergy (Berg, Bennich & Johansson, 1971; Stenius *et al.*, 1971; Pepys, Roth & Carroll, 1975), but somewhat lower than reported by others (Ahlstedt *et al.*, 1974; Eriksson, Ahlstedt & Belin, 1976). We found discordant results in patients with a low *in vivo* sensitivity. This might reflect the heterogeneity of the allergen preparations used for the *in vivo* tests and RAST (Pepys *et al.*, 1975; Eriksson *et al.*, 1976). These results could also be explained by insensitivity of the Phadebas RAST, since the radiolabelled anti-IgE used in this study had both D_{e1} and D_{e2} specificity. With a more sensitive RAST method, using isotope-labelled D_{e2} , a number of patients with low-grade allergy might have been discovered (Deuschl & Johansson, 1977). An alternative explanation for a negative RAST in patients with a positive clinical diagnosis could be a localized allergy, with local production of reagins (Huggins & Brostoff, 1975; Merrett *et al.*, 1976). This is further supported by the finding that in these patients also there was a clear, albeit clinically insignificant, rise in the specific IgE antibody level after the following birch pollen season (Viander, 1977).

After a 2 year immunotherapy, the total seasonal symptom scores of both the treated and the untreated patients were significantly correlated with the pre-treatment nasal sensitivities and with the RAST results. This is in agreement with earlier findings that the seasonal symptoms of untreated and treated patients correlate with the degree of nasal sensitivity (Feinberg, Stier & Grater, 1952), the serum skin-sensitizing antibody titres (Connell & Sherman, 1967), the sensitivity of the patient leucocytes to challenge with specific antigen *in vitro* (Lichtenstein *et al.*, 1966) and the level of the specific IgE antibody in the serum (Lichtenstein *et al.*, 1973), but not with direct skin testing (Connell & Sherman, 1967). Our findings show that in patients with verified pollen allergy, the clinical sensitivity in terms of the RAST or a graded nasal test may be used as a predictor of the severity of the seasonal symptoms.

There are few reports on the correlation between the clinical sensitivity of the patients and the appearance of the first seasonal symptoms. Hyde (1972) estimated that '10% of hay fever patients are likely to have symptoms when the pollen count exceeds $10/m^3$ '. The most sensitive patients have reported symptoms even before pollen can be detected by Hirst traps (Davies, 1975). These findings are consistent with those of this study: 13% of the treated patients and 16% of the untreated ones reported symptoms with pollen counts exceeding $19/m^3$. Furthermore, the appearance of the first symptoms at pollen counts of less than $30/m^3$ was significantly associated with a high clinical sensitivity in the patients.

According to Frankland & Davies (unpublished results, see Davies & Smith, 1973), all clinically sensitive patients experience symptoms of hay fever when the grass pollen count exceeds $50/m^3$. Similar results were obtained by Ogden & Lewis (1960) and by Fuckerieder (1976). In the present study, 90% of both the treated and the untreated patients had symptoms when pollen count exceeded $80/m^3$. The larger amounts of birch rather than grass pollen required to provoke symptoms in all clinically sensitive subjects could be explained by the smaller size of birch pollen, resulting in a much smaller average volume in birch pollen than in grass pollen (Hyde, 1972). Thus with the same number of grass and birch pollen spores, quite different concentrations of pollen allergen per m^3 of air will be obtained. An alternative explanation would be different allergenicity of different pollens and a different speed of release of allergens from different pollen grains in the nasal mucosa (Marsh, 1975).

A high proportion of the patients, irrespective of their clinical sensitivity, continued to have symptoms late in the pollen season, when the pollen counts were low. High symptoms in relation to pollen counts late in the ragweed season have been reported previously (Lichenstein *et al.*, 1966; Sack & Golan, 1942). A probable explanation for this phenomenon would be a decreased nasal threshold after the environmental exposure to pollen, 'the priming of the end organ' suggested by Connell (1968). Thus the existence of symptoms at low pollen counts reflects the high nasal sensitivity of the patients only early in the pollen season, not late in the season.

The hyposensitization therapy did not affect the mild symptoms. On the contrary, the immunotherapy decreased significantly the occurrence of severe symptoms in the early season and during the peak pollen season. These findings agree with earlier findings: total disappearance of symptoms after hyposensitization therapy is rare, and the severity of daily symptoms of the treated patients is significantly less than that of the untreated patients only in periods of high pollen counts (Lowell & Franklin, 1965; Norman *et al.*, 1968). The alleviation of the symptoms of treated patients on days with high pollen counts reflects a reduction in the nasal mucous membrane sensitivity after immunotherapy (Feinberg *et al.*, 1952; Fagerberg, Nilzén & Wilholm, 1972). Our future studies will deal with the relationship between the immunological changes during immunotherapy and the amelioration of the clinical symptoms.

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