

Changes in skin and nasal sensitivity to allergens and the course of rhinitis; a long-term follow-up study

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Background: Allergic skin test reactivity tends to decrease with aging, but whether the decrease is associated with changes in symptom severity and duration of the disease or determined only by aging, is poorly understood.

Objective: Our aim was to analyze skin test sensitivity some 20 years after primary testing and to relate possible changes in reactivity to aging, duration of rhinitis, and changes in severity of rhinitis symptoms.

Methods: One hundred and seven rhinitis patients who had been investigated earlier were re-interviewed and their current allergy re-assessed after a follow-up of 23 years. All patients were skin prick tested with 22 to 26 common allergens. The allergic rhinitis status was verified with nasal allergen challenge.

Results: Skin test reactivity showed a significant trend decreasing towards older age groups over the period between the two investigations. Rhinitis symptoms tended, on average, to become milder during the follow-up, but an association between skin test reactivity and changes in symptom severity could not be verified.

Conclusions: Rhinitis symptoms tend to become milder and the allergic skin reactivity usually decreases in the long run, but these changes may occur independently of each other. In this study, the change in rhinitis symptom severity seems not to be related to the decrease in skin test reactivity.

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INTRODUCTION

Allergen skin test reactivity is a common diagnostic parameter for verifying allergic rhinitis and other allergic diseases. The epidemiology of skin test results as compared with clinical disease has been previously studied.¹ In a cohort study with repeated evaluations, Barbee et al² showed that although there was an overall increase in skin test reactivity over a period of 8 years, aging tended to reduce skin reactions. To our knowledge, there are no detailed reports on the association between skin test results and aging in the

light of the duration of the disease and changes in symptom severity. In a previous interview study, we found a trend of decreasing symptom severity in allergic and nonallergic rhinitis of long duration.³ In this follow-up study, we have compared the results of skin tests and nasal provocation in the same series of rhinitis patients tested on two occasions more than 20 years apart.

PATIENTS AND METHODS

Patients

The patient series was collected among patients enrolled in an earlier study of non-infectious allergic and nonallergic rhinitis. All patients had initially in 1969–1972 undergone a fixed set of investigations including history taking, allergy testing with scratch or intracutaneous tests, nasal provocation, and otorhinolaryngological examinations.^{4,5} The number of patients in the initial series was 770. In 1989, 180 of them took part in a questionnaire study

designed to evaluate the course of their rhinitis symptoms.³

In 1993 to 1994, 107 of these patients (61 women and 46 men, mean age 51 years, range 27 to 78 years) participated in the present study for assessment of long-term changes in the rhinitis and allergy status after an average follow-up of 22.9 years (range 20.4 to 25.0 years). Information on the onset and duration of rhinitis symptoms, changes in rhinitis symptom severity, present and past history of nasal disorders, operations of the nose and paranasal sinuses, therapy received for rhinitis, and smoking habits was gathered with the help of a questionnaire completed by all patients.

The study protocol was approved by the ethics committee of the clinic. All subjects gave their informed consent with regard to participation in the study.

Allergy Tests in the First Study in 1969 to 1972

The following allergens were included in the initial skin tests and the results were available for the follow-up analysis: birch (95 patients), grass species (timothy or meadow foxtail, 95), Compositae species (dandelion, Chrysanthemum species, and mugwort, 90), house dust or *Dermatophagoides* species (95), animal dander (horse, cow, dog, and cat, 83), chicken feather (78), wool (78), mold mix (76), and food allergens (hazelnut, egg, fish, and cow milk, 45 patients). In grading the test results, a scale from “–” to “++++” was used, “+” indicating a wheal the diameter of which was at least 25% of the diameter elicited by the positive histamine control and “++” indicating a wheal with a diameter at least 50% of the positive control. The criterion for a

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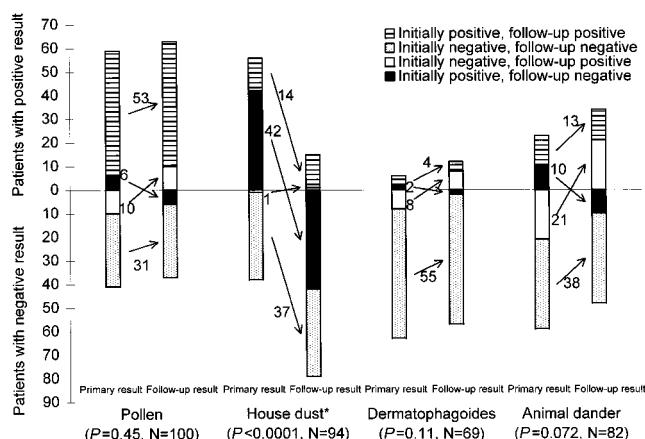


Figure 1. Changes in skin test positivity of 106 rhinitis patients during the follow-up period of 23 years. Numbers of positive reactions to different allergens shown with P values of McNemar's test. *Dermatophagoides tested instead of house dust in the follow-up study.

positive skin test was a reaction greater than "+".

The nasal provocation was considered positive when at least two of the following criteria were met after challenging the nose with allergen: itching, sneezing, discharge, subjectively noted obstruction of the nose or a rhinoscopic finding of changes in the nasal mucosa (swelling or color change) or an increase of 25% or more in total nasal resistance as measured by active posterior rhinomanometry.^{6,7} The patient was considered allergic, if he or

she had at least one positive skin test confirmed by positive nasal provocation.

Allergy Tests in the Present Follow-up Study

Skin prick tests were performed with Soluprick® allergen solutions (ALK, Denmark). All patients were tested with 22 to 26 common allergens, including birch, alder, meadow foxtail, orchard grass, meadow fescue, ryegrass, timothy, Kentucky bluegrass, mugwort, dandelion, horse, dog, cat, and cow dander, wool, chicken feather,

Dermatophagoides farinae and *ptero-nyssinus*, *Alternaria alternata*, *Candida albicans*, *Cladosporium herbarum*, guinea pig, latex, egg, fish, and cow milk. The patient was considered prick test positive if at least one allergen elicited a wheal with a diameter at least 3 mm larger than that of the negative control.

Nasal allergen provocation was performed on all patients who had previously been considered allergic, were prick test positive, or had a positive history of allergic symptoms possibly caused by some specific allergen. At the beginning of the session, anterior rhinoscopy was performed and the amount of mucus and degree of conchal swelling were recorded. The nose was first challenged with the diluent of the allergen extract (ALK-Diluent®, ALK, Denmark). Assessments were made 15 minutes after the diluent test and 15 and 30 minutes (and 45 minutes for house dust mite allergen) after challenging with Aquagen® SQ (ALK, Denmark) aqueous allergen solution unless a positive reaction had been recorded earlier. The provocation was made bilaterally with a spray dose of 0.1 mL. In most cases, a concentration of 100,000 SQ units per mL (SQ-U/mL) was used. In seven cases in which an exceptionally strong reaction was anticipated, 1,000 SQ-U/mL was used first and, if needed, a stronger solution later. The degree of rhinorrhoea⁸ and conchal swelling were graded in each nasal cavity on a 3-point scale (none—mild—considerable). The number of sneezes between the provocation and recording was counted. Possible presence of other symptoms or signs (ie, tearing, pharyngeal swelling, ear blocking, conjunctival redness, urticaria, cough, and dyspnea) was registered.

In conjunction with all assessments, nasal resistance was measured on each side at 150 Pa pressure and total nasal resistance (TNR) calculated using a RhinoComp® computerized active anterior rhinomanometer.

The recorded changes were converted into a provocation result score as described in Table 1 (slightly mod-

Table 1. The Score of Nasal Allergen Provocation

Allergen Provocation	Score
Average increase in nasal discharge	
None	0 points
Change from none to mild or mild to considerable on at least one side	1 point
Bilateral reaction, change from none to considerable on at least one side	2 points
Average increase in swelling of the inferior turbinates	
None	0 points
Change from none to mild or mild to considerable on at least one side	1 point
Bilateral reaction, change from none to considerable on at least one side	2 points
Irritation	
0–2 sneezes	0 points
3–5 sneezes	1 point
6 sneezes or more	2 points
Remote symptoms	
Tearing, pharyngeal swelling or ear blocking	1 point
Conjunctival redness, urticaria, cough or dyspnea	2 points

ified after Albegger⁸). The provocation was considered positive if a score of at least 3 points was achieved or if the patient got 2 points but TNR increased at least 50% compared with the measurement after the diluent challenge.

Statistical Methods

McNemar's test was used to analyze paired dichotomous data. Fisher's exact test, Pearson's chi squared test, and chi squared test for trend were used to analyze independent categoric data. For this purpose, the patients were divided into thirds with tertiles of age at the time of the follow-up study.

RESULTS

One hundred and six patients were tested. One patient was excluded because of no recordable reaction to any substance, including the histamine control.

The detailed records of reactions to different allergen groups are presented in Figure 1. Twenty-one patients had developed a new positive skin reaction to animal allergens, while 10 patients had changed from positive to negative ($P = .072$, McNemar's test). For the pollen and *Dermatophagoides* allergen groups, the differences were less significant. In contrast, comparison of the initial house dust reactions with the present house dust mite results showed a clear difference: only one previously negative patient had become prick test positive, but in 42 patients the discordance was in the opposite direction from positive to negative ($P < .0001$). Forty-eight of the 56 patients with positive skin test reaction to house dust in the initial study had also been tested for animal danders. Twenty-nine (60%) had showed at least one positive reaction. In the present study, 21 of these 56 patients (38%) showed no prick test reaction to any animal or house dust mite allergen.

The distribution of the patients by age at follow-up and the changes in the skin test reactivity over the follow-up period are presented in Figure 2. In the initial tests in 1969 to 1972, 83 patients (78%) had at least one positive skin test result. In the present study, 68

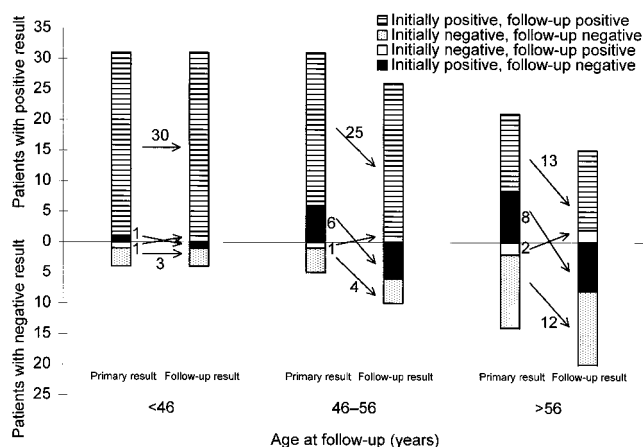


Figure 2. Changes in allergen skin test positivity during the follow-up period of 23 years. Numbers of skin test positive and negative patients distributed by age groups.

(82%) of them showed at least one positive prick test reaction, but 15 (18%) were prick test negative. Of the 23 initially skin test negative patients, 4 had at least one positive prick test reaction in the present study ($P = .022$, McNemar's test). If we exclude the patients with a positive reaction to only house dust in the initial study, it appears that 68 of 91 patients (75%) had had at least one positive skin test result in the first study, and that 8 of them (12%) were prick test negative some 20 years later. As regards the four initially negative patients with positive follow-up tests, the difference was not significant ($P = .39$).

Nasal provocation was positive in 74 (89%) of 83 skin test positive patients in the primary study. A new nasal challenge was made on 67 of these 74. Fifty-one (76%) still had a positive reaction, two of them now being prick test negative, but in 16 (24%) the challenge was negative. Sixty-one (82%) of the 74 initially provocation positive patients were still prick test positive. Seven patients with initially verified allergy were excluded from the challenge analysis: three refused and for four the appropriate allergens for provocation were not available. The details are shown in Figure 3.

There was a significant downward trend in prick test positivity with advancing age both in the whole series and in the patient group with initially

confirmed allergy. In the third of the youngest patients, 31 of 35 (89%) had at least one positive prick test reaction, whereas the corresponding figures were 26 of 36 (72%) and 15 of 35 (43%) in the middle and oldest thirds ($\chi^2_{\text{trend}} = 16.79$, $P < .0001$). In the group of allergic patients, the percentages were 97, 79, and 63 ($\chi^2_{\text{trend}} = 8.86$, $P = .0029$). The average duration of rhinitis symptoms was 31 (SD 8.6) years. No downward trend in skin reactivity could be seen, when the patients were divided into thirds according to duration of rhinitis symptoms (58% to 78% prick test positive, $\chi^2_{\text{trend}} = 0.029$, $P = .87$).

A significant downward trend was also apparent when we assessed the proportions of allergy, as verified by nasal challenge in the three age groups. These results are depicted in Figure 4.

Ninety-two patients (92%) reported that they still had symptoms of rhinitis and eight (8%) that symptoms no longer occurred. Of those who still had symptoms, 64 now reported milder, 18 equally severe, and 16 more severe symptoms. There was no difference in the proportions of prick test positive patients between the groups with different symptom changes, the percentage being 64 to 75 ($\chi^2_{\text{trend}} = 0.38$, $P = .54$) in the whole series and 77 to 100 ($\chi^2_{\text{trend}} = 2.24$, $P = .13$) in the patient group with initially verified allergy. The details are shown in Table

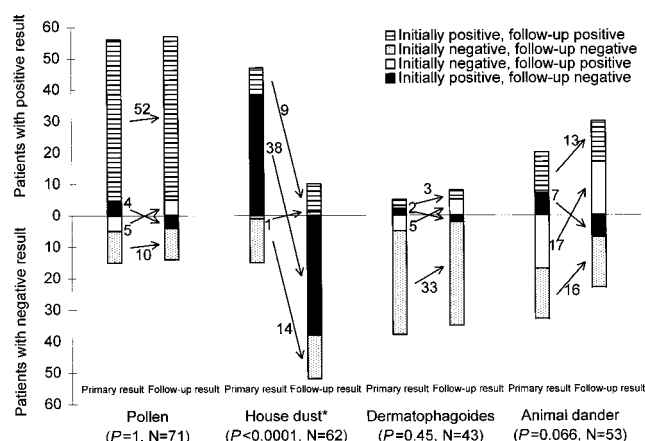


Figure 3. Changes in skin test positivity of 74 patients with initially verified allergic rhinitis during the follow-up period of 23 years. Numbers of positive reactions to different allergens shown with *P* values of McNemar's test. *Dermatophagoides tested instead of house dust in the follow-up study.

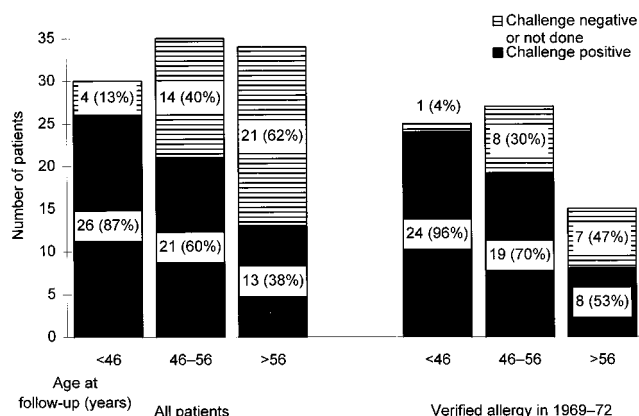


Figure 4. Age-related nasal allergen provocation results in the follow-up study. Numbers and percentages of challenge positive and negative subjects distributed by age in the whole series ($\chi^2_{\text{trend}} = 15.61$, $P = .0001$) and in the group of patients with initially verified allergy ($\chi^2_{\text{trend}} = 10.05$, $P = .0015$).

2. Twenty patients (19%) were current smokers, 33 (31%) ex-smokers, and 53 (50%) stated that they had never smoked. There were no differences in the proportions of prick test positive patients or patients with verified allergy between the groups of current smokers, ex-smokers, and non-smokers.

DISCUSSION

The main result of our study was that prick test reactivity showed a clear, decreasing trend in the older subjects and that there were no associations between this decrease and the duration of rhinitis symptoms or changes in symp-

tom severity. Rhinitis symptoms, however, tended to become milder in the course of time independently of prick test sensitivity.

This study probably reports on the longest period for which a large group of patients has been followed for allergic or nonallergic rhinitis. While a long observation period is likely to give a more accurate picture of changes, certain disadvantages become apparent. The number of patients in the first survey was 770, but only 23% of them took part in our questionnaire study 18 years later, and 14% in the present clinical follow-up study. Some of the patients had died, but presumably the main reason for lack of compliance was moving to another area or unwillingness to be re-investigated. It is plausible that patients whose symptoms have become milder will be more reluctant to participate. If this is the case, the actual proportion of patients with a favorable outcome is greater than our results suggest.

At the time of the first study between 1969 and 1972, the skin prick test was not a common method in allergy diagnostics. The more sensitive and less specific intracutaneous and scratch tests were usually used; therefore, when classifying the patients as allergic or nonallergic in the first study, we used a rather stringent criterion of a positive skin test confirmed by positive nasal provocation. Comparison of the initial results with those obtained in the present study may thus be considered fairly reliable. Re-testing with intracutaneous or scratch tests to achieve better comparability would, on the other hand, have been inappropriate, because similar allergen extracts are no longer available and the greater sensitivity of the method

Table 2. Results of Skin Prick Tests and Changes in Rhinitis Symptom Severity in 106 Patients Participating in a Follow-up Study 23 Years After Initial Examinations

	Whole Series (N = 106) Prick-test		Patients with Initially Verified Allergy (N = 74) Prick-test	
	Positive	Negative	Positive	Negative
Total remission	6	2	5	1
Symptoms still occur				
Have become milder	41	23	34	10
Are equally severe	13	5	11	2
Have become worse	12	4	11	0

would, nevertheless, have led to poorer specificity. It is difficult to reconstruct with certainty the composition of the old house dust extract, but it is likely that most of the irreproducible, probably nonspecific and irritative reactions elicited by the extract have been other responses than those caused by house dust mite allergy.

The test results recorded in the initial study did not describe any definite sizes of skin reactions, but a semiquantitative scale of “+” and “-” signs was applied. In the present study, the more up-to-date millimeter scaling was used and the reaction was regarded as positive, if at least a 3-mm wheal was present; thus, the results of the two test series are not completely comparable.

In the skin test responses, significantly more changes had occurred from positive to negative than vice versa. The main reason for the difference seemed to be the large number of probably nonspecific house dust reactions. When these reactions were excluded, the difference essentially disappeared. In the majority of patients the condition was unchanged. A more detailed comparison of different allergen groups revealed more changes, however, indicating that while reactivity to some allergens decreased the patients developed new reactions. New allergies were found especially for animal danders. The reason for this phenomenon could be the growing popularity of home pets during the follow-up period.

Repetition of skin testing is sometimes criticized on the grounds that changes in reactivity seldom occur. According to our results, there may be changes and a new series of skin tests can give valuable information in selected cases, where a clear suspicion of new allergy exists.

Barbee et al² have reported a higher prevalence of skin test reactivity among ex-smokers than among smokers or nonsmokers. In our series, no significant differences between these groups could be seen. It is possible that the long follow-up period per se had such an impact on skin test reactivity that a minor difference between various smoking status groups was not revealed.

In clinical work, the physician often meets a patient who wants to know, how his rhinitis is going to develop in the long run. Our results indicate that rhinitis symptoms generally tend to become milder and that allergic reactivity usually decreases, but changes in symptom severity are not directly associated with test results.

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