Local Allergic Nasal Reactions Convert to Classic Systemic Allergic Reactions: A Long-Term Follow-Up

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Key Words

Local allergy · Nasal allergen challenge · Rhinitis · Skin test · Antigen-specific IgE

Abstract

Background: There is poor knowledge about the evolution of the negative skin test in local allergy over time. Does the negative skin test of patients with local allergies remain negative permanently or does it become positive? **Methods:** We describe our long-term observation concerning the evolution of the negative skin test over time. This is a retrospective, follow-up study using data from the medical records of a group of patients with local allergy. A total of 42 patients aged between 3 and 70 years (median age: 31.5 years) were studied. The duration of follow-up varied from 1 to 27 years. Skin tests were performed using the skin-prick test and intracutaneous techniques for pollen, molds, mites, feathers (goose and duck) and animal danders. Nasal provocation tests were conducted with the same allergens. Additionally, specific IgE in 17 patients was measured by enzyme allergosorbent test. **Results:** During the period of observation, the negative skin test reactions converted into positive reactions in 17 patients (40%). In addition to the negative skin reactions, 55% of the patients also presented positive skin reac-

tions. The conversion rate was higher in children and adolescents than in adults. In 4 patients, conversions occurred >7 years after the initial examination. Specific IgE was negative in all but 2 patients, in whom the conversion in the skin test was accompanied by a switch from negative to positive specific IgE. **Conclusion:** Conversions from local to classic systemic respiratory allergic reactions appear to be a common phenomenon.

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Introduction

Local allergic rhinitis is characterized by a positive response to the nasal allergen provocation test while the skin test reaction (skin-prick test (SPT) or intracutaneous (i.c.)) to the same allergen is negative. Specific IgE identified using the enzyme allergosorbent test (EAST) can be detected in nasal secretions but not in the serum of these patients [1]. This type of allergy is limited to the nasal mucosa and therefore referred to as local allergic rhinitis [2, 3], entopy [4] or allergic rhinitis with a negative skin test [5]. Clinical symptoms, nasal secretions and the profile of cytokine production of local allergic rhinitis are similar to classic allergic rhini-

Table 1. Skin tests and specific IgE in patients with positive nasal provocation test and whose skin tests converted from negative to positive

No.	Age, years ^a	Elapsed time from initial skin test		EAST class ^b	Allergen	SPT/i.c.
		to last negative skin test ^c	to first positive skin test			
1	53	7	27		mites	i.c./i.c.
2	36	7	10		mites	i.c./i.c.
3	6	8	13		tree pollen	SPT/i.c.
4	25	11	14		grass pollen	SPT/SPT
5	55	–	11		mites	i.c./i.c.
6	3	4	8	0/4	mites	SPT/SPT
7	5	3	4	0/n.p.	mites	SPT/i.c.
8	21	–	2		tree pollen	i.c./i.c.
9	18	–	5	n.p./0	mites	i.c./i.c.
10	33	–	17	n.p./0	mites	i.c./i.c.
11	11	1	8	0/0	grass pollen	i.c./i.c.
12	38	5	8	n.p./0	grass pollen	SPT/SPT
13	25	1	4	0/0	tree pollen	SPT/SPT
14	42	–	12		feathers	i.c./i.c.
15	11	–	2	n.p./0	tree pollen	SPT/SPT
16	42	2	7	0/0	grass pollen	SPT/SPT
17	5	1	2	n.p./2	grass pollen/dog	SPT/SPT

n.p. = Not performed.

^a At first skin test.

^b First result at time of first negative skin test/second at time of positive skin test.

^c Intermediate skin test.

tis [6, 7]. In many patients with local allergic rhinitis, associations with conjunctivitis and asthma are frequent [7, 8].

Very little is currently known about the long-term evolution of negative skin test reactions in local allergies [8, 9]. In 1987, we observed local allergic reactions in 102 patients [10]. In 15 of these, we conducted a second skin test within 3 years; 6 patients reacted positively in this second test. Compared to classic allergic reactions, our patients with local allergies experienced symptoms for shorter periods [10].

In 2014, Rondón et al. [8], however, reported on 194 patients with local allergic nasal reactions in Spain, for whom only 6.8% of the negative skin tests became positive within 5 years. This was not significantly more frequent than in nonatopic controls (4.5%).

Considering how our results differed from those of the study by Rondón et al. [8], the question arose as to whether the higher rate of conversions to positive skin tests that we observed would be confirmed when observing a greater number of patients over a longer period of time. We were also interested in examining the specific serum-IgE levels in such patients.

Patients and Methods

In this retrospective, follow-up study, we collected the clinical records of patients who had had a positive reaction to nasal allergen provocations and a negative skin test reaction to the same allergen between 1982 and 2012 at the Malteser Lungen- und Allergiezentrum Bonn (Praxis Prof. Sennekamp, Bonn, prior to 2007). We selected 42 patients who had repeated the skin test once or several times in the years following the first test. Most of these patients had also been evaluated in a previous study [10]. Eighteen patients were ≤25 years old and 24 patients were >25 years old. Out of the total of 42 patients, 25 (60%) were female. All patients had had seasonal or perennial allergic symptoms in the upper and/or lower airways and had been treated accordingly. Skin tests were performed by the usual modified SPT or i.c. techniques [11]. Five patients had positive nasal tests for more than one allergen with negative skin reactions (tables 1, 2).

Skin tests were conducted on all 42 patients for mixtures of grass pollen, tree pollen (birch, hazel and alder), weed pollen (mugwort (*Artemisia vulgaris*), plantain, orache, goosefoot and nettle), rye pollen, *Alternaria*, *Aspergillus*, *Penicillium*, *Cladosporium*, *Mucor* and *Fusarium*, the mites *Dermatophyoides pteronyssinus* and *D. farinae*, a mixture of feathers (goose and duck) and two mixtures of animal danders (dog, cat, horse, rabbit, goat and sheep). Additional skin tests (e.g. for food allergens) conducted on these patients were not considered in this study.

The panel of allergens used for nasal provocation contained grass pollen mix, tree pollen mix (birch, hazel and alder), *D. ptero-*

Table 2. Skin tests and specific IgE in patients with positive nasal provocation and whose skin tests remained negative

No.	Age, years ^a	Elapsed time between initial and last skin test	EAST class ^b	Allergen	SPT/i.c.
1	3	1		mites	SPT/SPT
2	9	5		grass pollen	SPT/SPT
3	56	3		cat	i.c./i.c.
4	13	1		grass pollen/tree pollen	i.c./i.c.
5	42	2		mites	i.c./i.c.
6	40	5		dog	i.c./i.c.
7	51	11		mites	i.c./i.c.
8	30	2	–/0	mites	i.c./i.c.
9	35	14	–/0	mites	i.c./i.c.
10	30	10	0/0	mites	i.c./i.c.
11	22	1		mites	i.c./i.c.
12	21	13	–/0	mites/sheep wool/cat	i.c./i.c.
14	51	10	–/0	feathers	i.c./i.c.
15	48	5		sheep wool	i.c./i.c.
16	24	9		grass pollen	SPT/i.c.
17	46	9		mites	i.c./i.c.
18	17	3		mites	i.c./i.c.
19	44	3		mites	i.c./i.c.
20	70	3	0/0	mites	i.c./i.c.
21	55	3		grass pollen	i.c./SPT
22	28	2		mould	i.c./i.c.
23	59	8		mites	i.c./i.c.
24	42	9	–/0	mites/sheep wool	i.c./i.c.
25	44	11		mites	i.c./i.c.

^a At initial skin test.

^b First result at time of initial negative skin test/second at time of later skin tests.

nyssinus, feather mix (goose and duck), cat, dog, sheep and a mold mixture (*Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, *Mucor*, and *Fusarium*).

Commercial allergens (Bencard) were used for the skin and nasal tests. Specific IgE determination via fluorescence enzyme immunoassay (FEIA), a special EAST, was performed using the Phadia (Pharmacia, Thermo-Fisher) CAP system (CAP-FEIA) according to the manufacturer's instructions.

Nasal challenges were conducted during an asymptomatic period by spraying the negative control solution into one nostril and the diluted allergen into the other nostril. When the control was tolerated without symptoms and without a change in the nasal resistance, the allergen was sprayed in diluted form. Depending on the anamnesis, the allergen was diluted at a rate of 1:1,000 (for heavy symptoms) or 1:10 (for slight symptoms). When the test was negative, the allergen dose rate was increased at most up to the undiluted allergen. Before the challenges and 2 and 10 min after spraying the control and allergen dilutions, symptoms (sneezing, rhinorrhea, itching, watery eyes, burning in the nose, an itchy throat and headaches) [10] were recorded, and nasal resistance was measured using rhinomanometry [12, 13]. For this purpose, the Siemens Siregnost FD5 measuring instrument was used in combi-

nation with the Hewlett-Packard x/y-reader, and different sizes of AMBU nasal masks. Provocation was deemed positive when nasal resistance rose to at least double its initial value and at least one clinical symptom appeared. When nasal resistance did not increase or rhinomanometry was impossible to perform (e.g. in young children), provocation was deemed positive when at least three symptoms appeared [10, 14–18].

Proportions were tested using the χ^2 test. For the comparison of continuous variables, the median and range are given and the nonparametric Wilcoxon rank-sum test was used. The probability of conversion was determined by product-limit Kaplan-Meier estimates. As the skin tests were not performed regularly, in the case of converted patients, the moment of conversion was estimated by the middle of the period from the last negative to the first positive skin test observed. Censored patients were considered with the time period until the last negative skin test. The survival distribution function of conversion is given and the probability of conversion is the difference to 1.0. For the comparison of Kaplan-Meier curves, the log-rank test was chosen. Age groups were defined as: ≤ 25 years and ≥ 26 years. Statistical significance was defined as $p < 0.05$. The statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, N.C., USA).

Table 3. Characteristics of the study patients

	Total (n = 42)	Conversion to positive skin test		Test between groups
		yes (n = 17)	no (n = 25)	p value ¹
Length of observation				
1–5 years	47.6 (20)	35.3 (6)	56.0 (14)	0.381
6–10 years	26.2 (11)	29.4 (5)	24.0 (6)	
>10 years	26.2 (11)	35.3 (6)	20.0 (5)	
Age ≤25 years	42.9 (18)	58.8 (10)	32.0 (8)	0.085
Age ≥26 years	57.1 (24)	41.2 (7)	68.9 (17)	
Local allergy to pollen	33.3 (14)	52.9 (9)	20.0 (5)	0.026
	Median (min.; max.)	Median (min.; max.)	Median (min.; max.)	p value ²
Length of observation	7.5 (1; 27)	8 (2; 27)	5 (1; 13)	0.169
Age	31.5 (3; 70)	25 (3; 55)	40 (3; 70)	0.075

All values are given as % (n).
¹ χ^2 test. ² Wilcoxon rank-sum test.

Results

A total of 42 patients were studied, and the duration of follow-up varied from 1 to 27 years. Nearly half were observed for ≤5 years (tables 1–3). Seventeen patients (40%, 8 males and 9 females) who initially had negative skin reactions converted to positive skin reactions at a later date (table 1). Once positive, reactions remained positive in further controls (not listed). In the remaining 25 patients (9 males and 16 females), all subsequent skin tests were negative (table 2). The duration of observation did not differ statistically between the conversion and nonconversion group (table 3).

The median of censored time to failure was 5 years and the estimated time to failure ranged from 1 to 17 years (median: 5.5 years). We observed that 25% of this population switched within 5.5 years and 50% within 10.5 years (fig. 1).

A trend was observed of more patients of <26 years old in the conversion group (table 3); the proportion of younger patients (≤25 years) with results that switched was 59% in comparison to 32% of the patients with persistent negative skin tests.

The age of patients whose test results switched from negative to positive ranged from 3 to 55 years, with a median age of 25 years at the initial test. The corresponding median age of the patients whose test results remained negative was 40 years, and their age at the initial testing ranged from 3 to 70 years. The difference in median age was not significant at a level of 5% ($p = 0.075$).

In the cohort study, the proportion of ‘switch’ patients was 56% (10/18) in young patients (≤25 years) in comparison to 29% (7/24) in older patients (≥26 years). The probability of conversion, given by Kaplan-Meier curves (fig. 2) was statistically significant higher for younger (≤25 years old) than for older patients ($p = 0.030$).

Pollen was the most frequent allergen (9 reactions) in the first group of patients whose skin reactions switched to positive, followed by mites (7 reactions; table 1). Conversely, mites prevailed in patients whose test results remained negative, with 15 reactions compared to 7 for pollen (table 2). Reactions to pollen at the initial test was statistically significant higher in the conversion group (53 vs. 20%, $p = 0.026$; table 3).

Eleven patients underwent additional skin tests in the period between the initial negative skin test and the positive skin test (table 1). All intermediate skin test results were negative. The time periods between the initial and intermediate skin tests are listed in table 3. The intermediate skin tests narrow down the period during which the conversion from negative to positive occurred. The switch from negative to positive took place at some point in time between the values in the first and second column of table 1. A review of the first 4 patients shows that the switch from negative to positive skin test was, at the earliest, 7, 8 or 11 years after the initial skin test.

Moreover, we observed positive skin reactions to at least one additional allergen of the applied skin test panel in 23 out of the 42 patients (55%). These reactions were

Fig. 1. Kaplan-Meier curve with 95% confidence interval. The time of conversion was estimated as the middle of the period between the last negative to the first positive skin test observed, or in censored patients as the time until the last negative skin test.

Fig. 2. Kaplan-Meier curves according to age group. The time of conversion was estimated as the middle of the period between the last negative to the first positive skin test observed, or in censored patients as the time until the last negative skin test.

more frequent in patients with converted skin reactions (76%, 13/17) than in patients with persistently negative skin tests (40%, 10/25).

Specific IgE was only detectable in 2 of 17 patients (mites, grass pollen) (12%; tables 1, 2). Skin tests of the two IgE-positive patients had converted from negative to positive skin reactions (table 1). No specific IgE, however, could be detected in patients whose skin tests remained negative (table 2).

Discussion

Our impression of a rather high conversion rate (6/15) [10] from negative to positive skin tests in local allergic rhinitis in our 1987 study was confirmed, with a conversion rate of 40%. As mentioned above, Rondón et al. [8] followed 194 patients with local allergy of recent onset and <2 years of evolution showing a lower conversion rate (6.8%) in adult patients and in 130 controls (4.5%).

In another study published in 2009, Rondón et al. [9] observed a conversion rate from negative to positive skin tests of 21% and serum-specific IgE in nonallergic rhinitis patients between 3–7 years after the initial evaluation. However, in that particular study, the presence of local allergic rhinitis was not explored by nasal provocation [9].

Our study describes, for the first time, a conversion from local to classic systemic allergic rhinitis >7 years af-

ter the initial evaluation. In contrast to the studies conducted by Rondón et al. [8, 9], this retrospective study did not involve a control group. The absence of a control group does not diminish the results of this study, because a conversion rate of 40% is an evident increase in comparison to the conversion rate in healthy subjects, i.e. only 17% of the population in the region where the study was conducted had positive skin tests on the aeroallergens tested here [19].

Based on the fact that 17 of the 42 patients followed in our study converted from negative to positive skin tests in an estimated time period of 1–17 years, it may be assumed that 50% will switch from negative to positive skin reactions within 10 years (fig. 1).

We frequently used i.c. tests, while Rondón et al. [8] invariably applied the SPT technique, which could influence negative skin test rates and rates of conversion. The more sensitive i.c. test may generate negative skin tests less frequently [20]. With regard to the specific IgE, the conversion rate of 12% observed in our study was higher than in their study (1.1%) [8], they did, however, test patients who were completely negative for all allergens. The explanatory power of our results may have been limited by the small number of patients.

Interestingly, pollen was the most common allergen in the group of patients whose skin tests converted from negative to positive, while there was a predominance of mites in patients whose skin tests remained negative (ta-

bles 1, 2). All in all, and congruent with the study by Rondón et al. [7, 8], house dust mites were the most frequent allergens, as evaluated in our previous study [10]. The predominance of the female gender in local allergic reactions was less pronounced in our study (60%) than in the study by Rondón et al. [8] (69%).

Those of our patients that had repeated skin tests remained symptomatic the whole time and were therefore in our long-time care. We cannot judge to what extent the patients who left our care became asymptomatic. In our 1987 study, local allergy patients had suffered from symptoms for an average of 2.5 years while those with classic systemic allergies had suffered for 4.5 years [10]. At that time, we had suggested that these local allergic reactions may be an early stage of classic allergic reactions. Our study demonstrates that younger patients (≤ 25 years old) with local allergies have a greater predisposition to acquire a systemic allergy than older patients (fig. 2).

Most of our patients with local allergies not only had local allergic reactions to ≥ 1 allergens but, in 55% of cases, also showed positive skin reactions to other allergens in the skin test panel. The Spanish patients in the study by Rondón et al. [8] were negative in the skin test for all applied allergens, so our patients differed in this respect, an important fact to take into account when considering the results of these studies.

Moreover, Simola et al. [21] observed that skin reactions in classic allergic rhinitis decline over time. This contrasts with our observation of increasing skin tests in local allergy.

Using allergen provocations with multiple aeroallergens, local allergic rhinitis, at 26%, is more common than nonallergic rhinitis (11%) [7, 22]. Rondón found classic allergic rhinitis to be the most widespread form of rhinitis at 63% [7]. The clinical symptoms of local allergic and classic allergic reactions do not differ significantly, except that the former have an earlier onset [7]. In nonallergic rhinitis, rhinorrhea and obstruction of the nose are more frequent, older patients predominate and there is no eosinophilia and no response to antihistamines [23].

Preliminary studies of immunotherapy suggest that patients with local allergic reactions benefit from this treatment [24–26].

Our above observations reinforce the role of nasal allergen provocation and the nasal detection of specific IgE antibodies in the diagnostics of local allergic reactions. Overall, if nasal provocation is more frequently applied as a result of our investigation, patients will have benefited from our insights, and this is particularly true when skin tests and specific IgE are negative.

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Disclosure Statement

The authors declare no conflicts of interest.

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