

Diagnostic significance of late cutaneous allergic responses and their correlation with radioallergosorbent test

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Summary

In order to study the clinical significance of late cutaneous allergic responses 178 intracutaneous tests were done on the forearm of forty-three allergic patients with perennial allergy and twelve patients with pollen allergy. The allergen concentration was chosen to give a moderate immediate response with a weal diameter of about 15 mm. Late cutaneous allergic responses (LCAR) were elicited in eighty-two intracutaneous tests in thirty-one patients with perennial allergy and in nine intracutaneous tests in eight patients with pollen allergy, with almost all the allergens frequently responsible for allergy in this area. Their occurrence was found to be related to the size of the immediate reaction. Almost all the patients showing LCAR had positive provocation tests and were clinically sensitive to the corresponding allergen.

Introduction

Ever since their introduction by von Pirquet, skin tests still enjoy the highest place in the diagnostic armamentarium of allergologists (Adkinson, 1981). In the diagnosis of underlying allergic processes it is important to observe the time of onset, duration and gross appearance of the skin allergic reaction to the antigen (Pepys, 1975). A type I reaction in the skin is characterized by a rapid development of a weal and flare response (Coombs & Gell, 1975). This attains its peak in 10–20 min and then subsides. Often a late diffuse oedematous response appears at the same site. The occurrence of these late cutaneous allergic responses (LCAR) has been known for many years, but little is known about their clinical significance. These responses have been considered to be mediated by IgG antibodies; however, many recent extensive investigations point out that this response is IgE-mediated (Solley *et al.*, 1976; Zetterström, 1978; Umemeto *et al.*, 1976; Dolovich & Little, 1972). This study was done to find out diagnostic significance, conditions for and frequency of their occurrence in the clinical practice as well as their correlation with radioallergosorbent tests (RAST).

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Material and methods

The study covers a group of 101 adults selected at random, ranging in age from 16 to 72 years, who because of asthma, rhinoconjunctivitis or a combination of these symptoms were referred for allergological investigation at the University Hospital, Uppsala, Sweden. To study LCAR with pollen allergens, twelve clinically sensitive patients of pollen allergy were later included in the study.

Skin tests with commercially available common allergens were carried out by an intracutaneous injection of 0.1 ml on the volar aspect of forearms. An allergen concentration calculated to give an immediate reaction with a weal diameter of approximately 15 mm was chosen with the help of end point titration using ten-fold dilutions performed on the back of the patients. Allergen concentrations from 1:1000–1:100 000 w/v were used. After instructions the patients measured the weals themselves at fixed intervals. As a rule the patients were seen after about 6 hr at the out-patient department, so that their readings could be confirmed and the nature of reactions observed. The reactions were graded as 0 if the sum of the perpendicular diameters was less than 10 mm, doubtful (+) if less than 20 mm, mild (++) if less than 40 mm, moderate (+++) if less than 80 mm and severe (++++) if more than 80 mm.

Blood samples were taken from every patient, allowed to clot, and the serum was separated and stored at -20°C until analysed. Total serum IgE levels were measured by paper radioimmunosorbent tests (PRIST) and the occurrence of specific IgE antibodies by RAST.

The RAST and PRIST tests were kindly performed by Professor S. G. O. Johansson at the Blood Center in this hospital with reagents obtained from Pharmacia Diagnostics, Sweden, in accordance with the enclosed instructions.

Depending on the case history, bronchial and nasal provocation tests were performed. Bronchial provocation tests were performed by inhalation of nebulized allergen solutions (Parinebuliser, West Germany). The test was started with inhalation of Coca's solution. In the absence of reactions, ten-fold increasing concentration of 1.0 ml allergen solutions were used until a positive reaction was obtained or until the most concentrated (1:10) allergen preparation gave negative results. The lungs were auscultated and peak expiratory flow rates (PEF) were checked before and after the tests. The response was considered positive if the peak expiratory flow showed a 20% fall or more and ronchi were heard. In nasal provocation tests a control test was administered by instilling 0.1 ml Coca's solution into one nostril. Increasing concentrations of allergens were used as in the bronchial provocation tests, until a positive reaction was obtained or until the most concentrated preparation gave negative results. The patients were observed for 20 min after instillation. The tests were considered positive if sneezing, pruritis and rhinorrhoea appeared.

Results

Diagnosis of cases established after careful evaluation of clinical history of allergic symptoms, intracutaneous tests, RAST, PRIST and provocation tests is given in Table 1. Out of 101 there were fifty-six atopics. In forty atopics with perennial symptoms and in three of the remaining forty-five patients considered to have intrinsic disease, immediate reactions of sufficiently large size were found on backs and further tests for occurrence of LCAR were done. Late cutaneous allergic responses (LCAR) were elicited in thirty-one cases in eighty-two intracutaneous tests with dust, mite and

Table 1. Diagnosis of cases studied and frequency of late reactions encountered in perennial allergies

Sample No.	Diagnosis	Total No.	No. of cases showing LCAR
1	Allergic rhinitis	43	23
2	Vasomotor rhinitis	27	—
3	Extrinsic bronchial asthma	7	7
4	Intrinsic bronchial asthma	18	—
5	Bronchial asthma + allergic rhinitis	6	3
	Total	101	33

animal danders in the patients with perennial allergy and in eight cases in nine tests with Birch and Timothy in the twelve patients with pollen allergy (Table 2).

Despite the attempt to achieve a standardized immediate response on the forearm, a wide variation from 8 to 30 mm mean diam. in the magnitude of immediate responses was obtained. The magnitude of the immediate response was found to be of great importance for the occurrence of a late response. Thus, in only three of the immediate responses of less than 10 mm diam., a late response was seen, while of thirty-nine cases with immediate responses of more than 15 mm diam. thirty-five gave rise to a late response. Moreover, there was a correlation between the size of the LCARs and immediate responses (Figs 1–4). In those who developed late responses, the r values and correlation coefficients were 0.88 ($P < 0.05$) for mites, 0.63 ($P < 0.001$) for animal danders, 0.25 (not-significant) for house dust and 0.81 ($P < 0.01$) for pollens. The correlation of RAST to LCAR is shown in Table 3.

The concentration of allergen needed to elicit an immediate response at intracutaneous skin testing showed strong correlation to the results of RAST. Nine out of forty-four showing positive immediate response with 1:1000 w/v strength of allergen had positive RAST. Positivity of RAST increased and sixteen out of eighteen showing immediate response to 1:100 000 or more had positive RAST results (Table 4). Since

Table 2. Distribution of allergens with which LCAR was encountered

Sample No.	Allergen	Total No. of tested cases	No. of cases showing LCAR
Perennial allergens			
1	Horse dander	43	10
2	Dog dander	43	23
3	Cat dander	43	21
4	Cow dander	43	7
5	House dust	43	13
6	House dust mite	43	8
Pollen allergens:			
1	Birch	12	6
2	Timothy	12	3

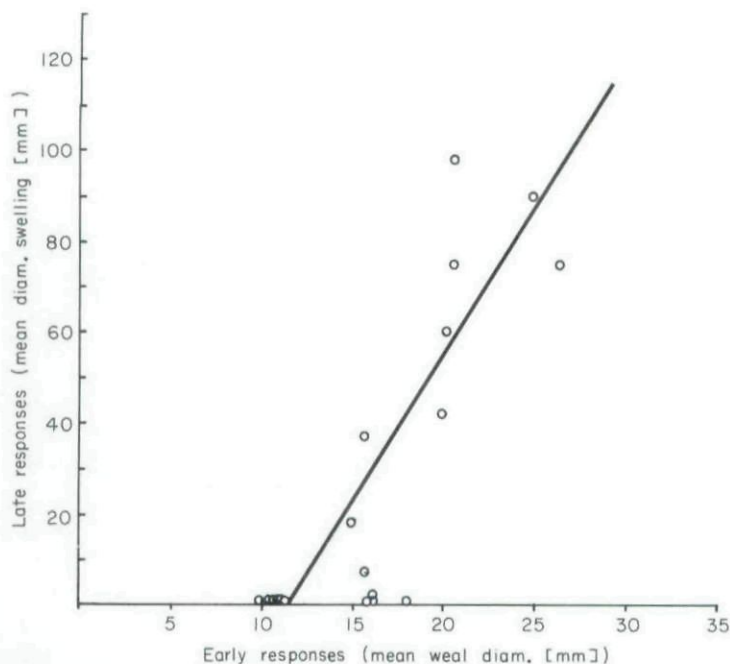


Fig. 1. Early and late cutaneous response to Birch and Timothy pollens. Weal diameters of early responses measured at 15 min are on the horizontal axis. Maximal mean diameters of LCAR are on vertical axis. There was statistically significant correlation between immediate and late responses and r values were 0.81 ($P < 0.01$).

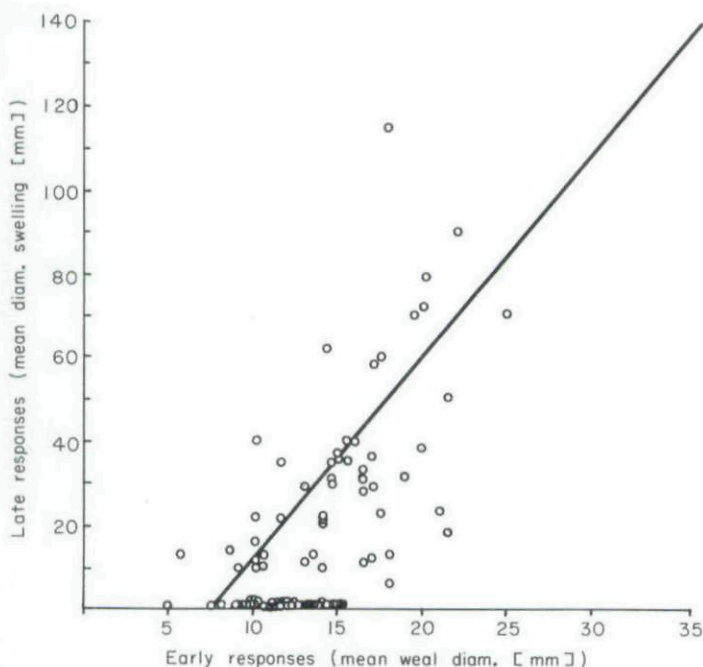


Fig. 2. Early and late cutaneous responses to animal danders. Weal diameters of early responses measured at 15 min are on the horizontal axis. Maximal mean diameters of LCAR are on the vertical axis. There was statistically significant correlation between immediate and late responses and r values were 0.63 ($P < 0.001$).

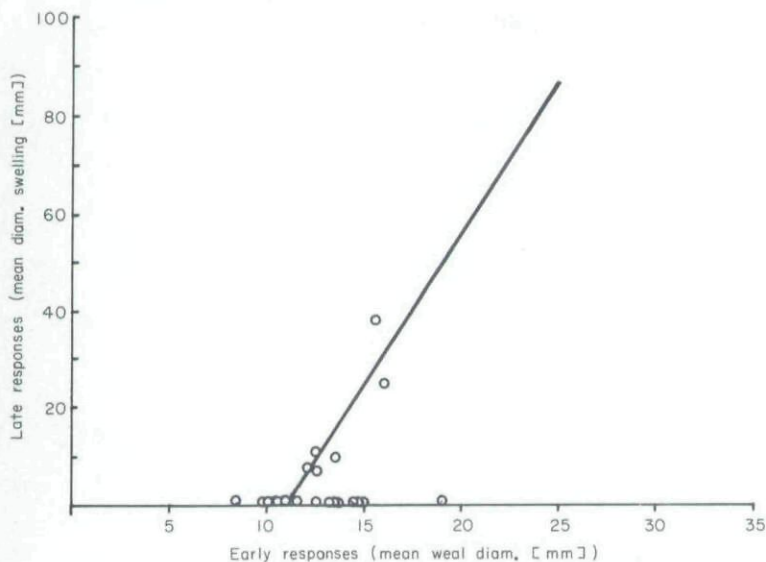


Fig. 3. Early and late cutaneous responses to *Dermatophagoides pteronyssinus*. Weal diameters of early response measured at 15 min are on the horizontal axis. Maximal mean diameters of LCAR are on the vertical axis. There was statistically significant correlation between immediate and late responses and r values were 0.88 ($P < 0.05$).

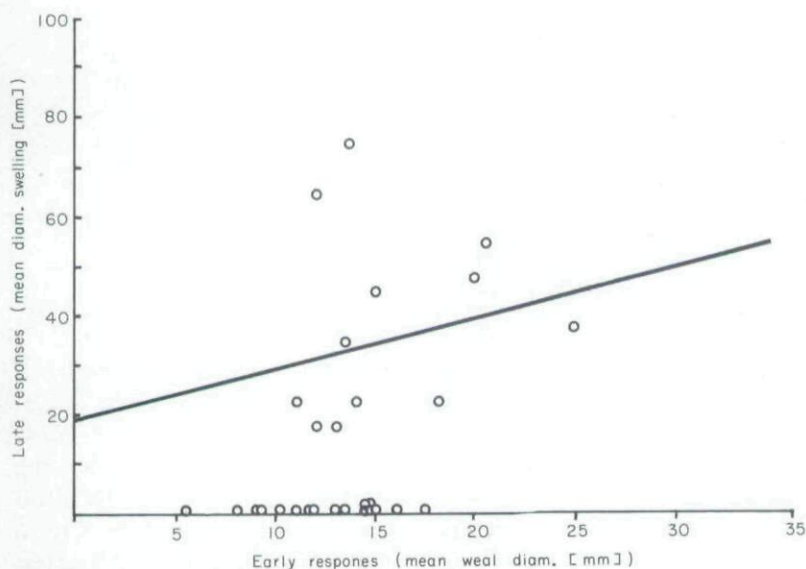


Fig. 4. Showing early and late cutaneous responses to house dust extract. Weal diameters of early responses measured at 15 min are on the horizontal axis. Maximal mean diameter of LCAR are on vertical axis. There was no statistically significant correlation between immediate and late responses and r values were 0.25 ($P = \text{NS}$).

Table 3. Relation between LCAR and in cases of perennial allergy

Strength of allergen	Severity of LCAR	Total No. of tested patients	Total No. of patients showing positive RAST
1:1000	+	4	1
	++	10	2
	+++	21	3
	++++	9	3
1:10 000	+	1	—
	++	5	1
	+++	6	1
	++++	8	5
1:100 000	+	1	1
	++	2	1
	+++	9	8
	++++	2	2
> 1:100 000	+		
	++	2	2
	+++	2	2
	++++		

Table 4. The relation of RAST to the strength of allergen with which response was elicited in cases of perennial allergy

Strength of allergen	Total No. of patients in which reaction was elicited	No. of cases showing positive RAST
1:1000	44	9
1:10 000	20	7
1:100 000	14	12
> 1:100 000	4	4

the dose of allergen was adjusted according to different skin sensitivities of the patients, magnitude of LCAR did not show any obvious correlation with positive RAST results (Table 5). In about one-third of the cases showing doubtful, mild and medium-sized LCAR, RAST was positive. This was also true in about a half of the cases showing large LCAR. The RAST results were positive in only 16 (22.2%) of the tests not eliciting LCAR. Provocation tests were performed in twenty-eight patients, with a total of sixty-eight allergens showing LCAR and seventy not showing LCAR. The test was positive with sixty-five allergens showing LCAR and forty-two not showing LCAR. Patients eliciting LCAR with high dilutions were found, at provocation test, to be positive at lower concentrations of the allergen (Table 6). The three patients, negative on provocations test, were showing LCAR to 1:1000 w/v strength of antigen and had weal size of less than 10 mm diam. Thus the magnitude of LCAR correlated well with the results of provocation tests and the clinical history.

Table 5. Incidence of positive RAST in relation to the severity of LCAR elicited in cases of perennial allergy

Severity of LCAR	Total No. of patients	No. of patients showing positive RAST
+	6	2
++	19	6
+++	38	14
++++	19	10

Table 6. Relation between LCAR and provocation test in cases of perennial allergy

Strength of antigen	Severity of LCAR	Patients with positive provocation test					Negative provocation test	
		≤1:10	≤1:100	≤1:1000	>1:1000	Total	test	Total
1:1000	+	2	6	—	—	8	3	11
	++	—	5	3	—	8	0	8
	+++	1	4	1	—	6	0	6
	++++	3	9	3	—	15	0	15
1:10 000	+	—	1	2	—	3	0	3
	++	—	3	2	—	5	0	5
	+++	—	2	1	—	3	0	3
	++++	1	1	4	—	6	0	6
1:100 000	+	—	1	1	—	2	0	2
	++	—	—	2	—	2	0	2
	+++	—	—	3	2	5	0	5
	++++	—	—	—	2	2	0	2
>1:100 000	+	—	—	—	—	0	0	0
	++	—	—	1	1	2	0	2
	+++	—	—	1	—	1	0	1

Discussion

The occurrence of an LCAR was strongly dependent on the magnitude of the immediate response. With the intracutaneous technique used in this investigation, a dose of allergen sufficient to give an immediate response of 10–12 mm was necessary in most of the cases. There was also a correlation between the size of LCAR and immediate response to mite, animal danders and pollen allergens. No significant correlation was found with house dust. This outcome may be due to a relatively low quality of dust extract. The slopes of regression curves were steep, implying that, once the pathogenetic mechanism of LCAR has started, it grows easily. This probably depends on the characteristics of the patient or properties of his or her inflammatory response. The importance of the patient's properties is shown by the fact that the same initial challenge with an immediate response of about 15 mm diam. gave rise to LCAR in some patients while in others it did not.

A strong correlation was found between the results of RAST and concentration of

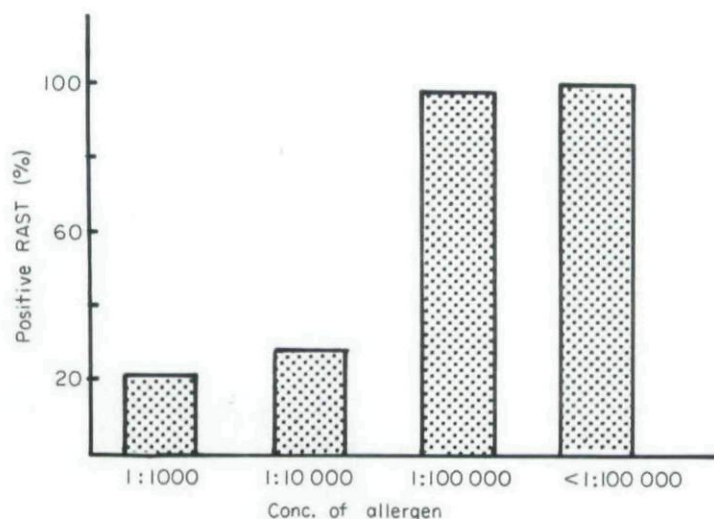


Fig. 5. Percentage of positive RAST in relation to concentration of allergen with which LCAR was elicited. Radioallergosorbant test (RAST) was positive in only 22% of the cases when LCAR was elicited with 1:1000 concentration of allergen. Positivity of RAST increased when LCAR was elicited with lower concentration of allergen.

allergen needed to elicit an immediate response. This is in agreement with many previous reports (Wide *et al.*, 1971; Norman, Ishizaka & Lichtenstein, 1973; Henderson & Gleich, 1974). However, a poor correlation was found between the occurrence of LCAR and the results of RAST. Since RAST does not detect low levels of specific-IgE antibodies (Adkinson, 1980; Gleich & Jones, 1975), these results indicate that either these LCAR were not mediated by IgE antibodies or that they were mediated by them, but the levels were low and therefore RAST was negative. We support the second view. The poor correlation that we have found is partially an effect of adjustment of allergen dosage when testing for LCAR on the forearms. In most of the patients with negative RAST, in spite of LCAR, tests were done with an allergen concentration of 1:1000. The positivity of RAST increased when LCAR could be elicited by lower dilutions of the allergen (Fig. 5). Moreover, a positive RAST was more often found with allergens eliciting LCAR than with allergens which did not elicit it. These findings suggest that LCAR can occur at relatively low levels of specific-IgE antibodies in the presence of high concentrations of allergen. Their dependence on the dose of the allergen is well recognized (Solley *et al.*, 1976; Umemoto *et al.*, 1976).

In the present study, LCAR were elicited with almost all the allergens frequently responsible for allergy in this area. Our findings support the opinion expressed by Solley *et al.* (1976) that they can be induced by any allergen.

In this study, LCAR was always associated with a positive provocation test and clinical sensitivity if more than 10 mm diam. A strong relation between clinical allergy and occurrence of LCAR has also been reported by Warner (1976). Simple observation of skin site for a few hours may be a valuable adjuvant in clinical investigation of allergic patients.

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