

Long-lasting allergic patch test reactions: a study of patients with positive standard patch tests

G. MANCUSO¹, R. M. BERDONDINI¹ AND G. CAVRINI²

¹Department of Dermatology of Municipal Hospital of Lugo, Ravenna

²Department of Statistical Sciences "P. Fortunati", University of Bologna, Italy

The purpose of this study was to determine the duration of patch test reactions and the frequency of long-lasting allergic patch test reactions (LLAPTR), and to identify the possible factors related to the development of the LLAPTR. For this purpose, a group of 263 patients positive to 1 or more allergens in the GIRDCA standard series was recruited. Readings were made for each patient 2 and 3 days after patch test application and continued every 2nd and 3rd day until the disappearance of all palpable erythema. The % of LLAPTR out of the total of reactions was high: 17.9%. Kathon CG was the hapten that caused LLAPTR most frequently, with 16 cases, a frequency of 76.1%, and a mean duration of the patch test reactions of 25.4 days. Risk factors investigated were age, sex, atopy, intensity of the patch test reaction and sensitivity to some allergens with the greatest number of positive patch tests. The relative importance of each risk factor was calculated by multivariate stepwise logistic regression analysis. It was found that a Kathon CG sensitivity was the most important risk factor for LLAPTR. 2nd was atopy, followed by strong patch test reaction. Rejected risk factors were sex, age and sensitivity to nickel sulfate, potassium dichromate, Disperse Blue 124, fragrance mix and p-phenylenediamine.

Key words: long-lasting allergic patch test reaction; risk factors; Kathon CG sensitivity; age; sex; atopy; strong patch test reaction. © Munksgaard, 1999.

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The term long-lasting allergic patch test reaction (LLAPTR) was adopted by Kanerva et al. (1) to indicate patch test reactions that persisted for 14 days or longer. Contrasting data are available on the frequency of LLAPTR. Kanerva et al. (1) believe that the majority of patch test reactions disappear within 5–10 days and rarely last longer. According to Todd et al. (2), LLAPTR are a common finding if reactions are checked by means of regular patient recall; in his experience, some 14.3% of patch test reactions persist as LLAPTR.

The pathomechanisms behind LLAPTR are unclear, but may involve either a localized persistence of the antigen (3) or a defect in cell-mediated immunity down-regulation mechanisms. Little is known about these down-regulatory mechanisms, but they may be mediated by suppressor T lymphocytes, anti-idiotypic antibodies, cytokines and HLA class II antigens (Ia)-expressing epidermal keratinocytes (1–5).

The aim of this study was to determine the duration of the patch test reactions and the frequency of LLAPTR and to identify the possible risk fac-

tors for LLAPTR. Risk factors investigated were age, sex, atopy, intensity of the patch test reaction and sensitivity to specific allergens. For this purpose, a group of 263 patients positive to one or more allergens in the GIRDCA standard series was assessed.

Patients and Methods

Over the period 1995–1998, a total of 798 consecutive patients, who were suspected of having allergic contact dermatitis, were patch tested with the GIRDCA standard series (30 substances, Firma, Italy): 317 patients were patch-test-positive. The GIRDCA standard series used in the 1990 version (6) essentially coincides with the European standard series (7); in particular, the concentrations and vehicles coincide for those allergens common to the 2 series, which in our study led to the highest number of positive patch tests (Table 1). All test substances were applied for 2 days (D) using the Al-test (Imeco AB, Sweden) on the patients' upper back and fixed with Scanpor tape

Table 1. Prevalence of LLAPTR (%) and mean duration of reactions to individual allergens^{a)}

Allergen	No. patch test pos.	LLAPTR (%)	Mean duration (days)
nickel sulfate ^{b)}	90	16.6	10.7±6.1
p. dichromate ^{b)}	40	2.5	8.4±4.4
Disperse Blue 124	29	13.8	10.1±4.9
fragrance mix ^{b)}	23	8.7	8.4±5.1
Kathon CG ^{b)}	21	76.1	25.4±12.8
p-phenylenediamine ^{b)}	21	4.7	8.5±4.0

^{a)} Allergens with the greatest number of positive patch test.

^{b)} Allergen also present in the European standard series.

(Norgesplaster, Norway). There were no eczematous lesions or otherwise damaged skin during patch testing. The 1st reading was made 1 h after removal, 2nd reading at D3. Reactions were scored according to the ICDRG scale (8). Final positivity was taken as the strongest reaction between D2 and D3. After the reading on D3, each of the 317 patch-test-positive patients were asked to participate in the study: 263 gave their consent. The group of non-participants was matched to the group of participants for demographic data including the MOAHL index (7) and distribution of positivity to the patch tests. The study consisted of the following:

- Checking of the positive patch tests every 2nd and 3rd day until positive reactions had disappeared. Duration of positive reactions was counted in days, starting from the day on which the test apparatus was removed until the disappearance of all palpable erythema. LLAPTR were defined as those showing + or greater response 14 days or more after removal of the test apparatus and NRAPTR as those reactions that showed no visible response at this time. No drug could be applied at the site of reaction; in reality, in some rare cases with particularly exudative reactions (+++), medication with boric acid 3% was recommended.

- Prick tests with major allergens: *Alternaria tenuis*, Compositae mix, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, Graminaeae mix, Parietaria mix, egg albumen and whole milk (Lofarma, Italy). Patients were considered to be atopic when they proved positive to one or more of the above-mentioned prick tests and/or had a positive history of asthma, allergic rhinitis or atopic dermatitis.

For statistical analysis, + positive patch test reactions were considered as weak, while ++ reactions were pooled with +++ reactions as strong positive reactions. LLAPTR and duration of patch test reaction were studied with reference to sex, age, atopy, initial grade of patch test positivity and sensitivity to some haptens in the standard series. For statistical calculation purposes, only the haptens most frequently the cause of contact sensitivity in our patients were considered: nickel sulfate (5% pet.), potassium dichromate (0.5% pet.), Disperse Blue 124 (1% pet.), fragrance mix (8% pet.), Kathon CG (0.01% aq.) and p-phenylenediamine (1% pet.). To evaluate the influence of each of these factors on LLAPTR, multivariate stepwise logistic regression analysis was performed using the LLAPTR as a dependent variable. From the results of the regression analysis, relative risks were computed as the probabilities of LLAPTR in the

Table 2. Prevalence of LLAPTR (%) and overall mean duration of patch test reactions by sex, atopy, intensity of the patch test reaction and age groups

	No. patch test pos.	LLAPTR (%)	Mean duration (days)
Sex			
male	69	21.7	12.3±8.4
female	298	17.1	11.8±8.0
Atopy			
atopic	74	44.5	15.8±7.6
non-atopic	293	11.2	10.7±7.9
Intensity of the patch test reaction			
strong	202	25.7	13.2±8.7
weak	165	8.4	9.9±6.7
Age groups			
≤30 years	113	15	10.6±6.5
31–60 years	157	19.1	12.7±8.7
>60 years	97	19.5	12.5±9.1

Table 3. Prevalence of LLAPTR (%) and mean duration of patch test reactions for individual allergens by atopic status

	Nickel sulfate	Potassium dichromate	Disperse Blue	Fragrance mix	Kathon CG
atopic	34.8% (12.8)	25.0% (14.8)	60% (16.2)	16.7% (10.8)	83.3% (24)
non atopic	10.4% (10)	0% (7.7)	4.2% (8.9)	5.9% (7.6)	66.7% (25.9)

Mean duration (days) of the reactions in parentheses.

presence of specific factors, versus the absence of the same factors. The statistical package used was SPSS for Windows, version 8.0. Comparisons were made using Student t-test for continuous variables and χ^2 -test for proportions. For all tests, $p < 0.05$ was assumed to indicate statistical significance.

Results

Out of 263 patients recruited for the study, 38, in spite of their initial consent, did not attend for the required readings and were therefore excluded. No significant differences were found with regard to sex, age, atopy and patch test positivity between the group of excluded subjects and those who completed the study. The latter group consisted of 225 subjects, 46 male and 179 female, aged between 4 and 80 years, with a mean age of 42. Each showed positive patch tests to 1 or more allergens, with a total of 367 reactions. 66 (17.9%) of these persisted as LLAPTR. Kathon CG and nickel sulfate were the allergens that caused LLAPTR most frequently, each with 16 and 15 cases, respectively; however, the incidence of LLAPTR as well as the mean duration of patch test reactions was significantly higher for Kathon CG (76.1%, 25.4 days, respectively) compared with the other substances tested (Table 1). There were no significant differences in LLAPTR frequency or duration of the patch test reactions with respect to sex and age

groups (Table 2). The frequency of the LLAPTR and the mean duration of the reactions were significantly greater in strong patch test reactions (+++, +++) (25.7%, mean duration 13.2 days, respectively) versus weak patch test reactions (+) (8.4%, mean duration 9.9 days, respectively). 46 subjects were positive to 1 or more of the prick tests carried out with the 8 above-mentioned allergens, while another 6 subjects, negative to the prick tests, had a positive history of asthma and/or allergic rhinitis. None were affected by infantile or childhood eczema or presented typical atopic dermatitis lesions. A total of 52 subjects were classified as atopic for the purpose of comparison with the patch test reactions. The frequency of LLAPTR was associated to an extremely significant extent ($p < 0.0000$) with atopy (Table 2), with a relative risk of the atopic subjects about 5× higher than non-atopic subjects. The mean duration of the patch test reactions was also significantly higher in atopic in comparison to non-atopic subjects, respectively 15.8 and 10.7 days ($p < 0.0001$). The influence of atopy varied for each allergen, with differences regarding the frequency of LLAPTR between atopic and non-atopic subjects that are significant for some substances, such as potassium dichromate ($p < 0.003$) and Disperse Blue 124 ($p < 0.0002$), and not for others, such as Kathon CG ($p > 0.05$) and nickel ($p > 0.05$) (Table 3).

In the multiple logistic regression analyses, Kathon CG sensitivity, atopy and strong patch test positivity were significant risk factors for LLAPTR (Table 4). The strongest risk factor for LLAPTR was Kathon CG sensitivity, with an odds ratio equal to 9.3; rejected risk factors were age, sex and sensitivity to nickel, potassium dichromate, fragrance mix, Disperse Blue 124 and p-phenylenediamine.

Discussion

The results of this study show LLAPTR occur in 17.9% of the total reactions, a value only slightly higher than that reported by Alderdice et al. (4) and by Bygum and Andersen (9), 14.3 and 17% respectively. These results confirm that LLAPTR are a common event if the reactions are checked by means of regular patient recall (2).

Table 4. Risk factors related to LLAPTR: results from multivariate logistic regression analysis

	OR	CI	p-value
Risk factors			
Kathon CG sensitivity	9.3	3.2–37.6	0.0001
atopy	5.2	2.5–10.8	0.0000
strong patch test reaction	2.5	1.2–5.4	0.0167
Rejected risk factors			
sex			0.9064
age (years)			0.1028
Sensitivity to:			
nickel sulfate			0.2413
potassium dichromate			0.6515
fragrance mix			0.4763
Disperse Blue 124			0.4692
p-phenylenediamine			0.9157

The odds ratio (OR) for each variable estimates the relative risk of LLAPTR; CI: 95% confidence interval.

Unlike what was observed for the other allergens, Kathon CG sensitivity was, in a logistic regression model, the strongest risk factor for LLAPTR (odds ratio 9.3). The LLAPTR so frequently observed with Kathon CG are difficult to explain. Hypothetically, metabolism and processing of the Kathon CG could differ from that of other allergens, resulting in a greater persistence of the allergen at the site of the reaction.

Risk factors for LLAPTR unrelated to specific allergen sensitivity are atopy and strong patch test reaction. Atopy is the 2nd risk factor for LLAPTR (odds ratio 5.2), although the importance differs for each allergen considered. The relationships between atopy and LLAPTR are still unclear. Regardless of its etiology, contact dermatitis can be prolonged and aggravated by the intranasal, subcutaneous or surface application of specific protein allergens to which an atopic individual has been shown to be sensitive (10). These observations indicate that for LLAPTR there could be a similar mechanism by which specific atopen can produce a constant flare-up of an existing, etiologically unrelated contact dermatitis at the site of the patch test in atopic individuals, regardless of whether the atopen reaches the skin by contact, ingestion or inhalation. Interestingly, a comparison between the atopic subjects with LLAPTR and atopic subjects without LLAPTR that we observed shows a higher frequency of multiple (2 or more) concomitant positive prick tests in the former with respect to the latter group, respectively 42.8% and 12.5% ($p < 0.03$). There are, on the other hand, no significant differences between the 2 groups regarding the nature of the prick-test-positive allergens, with a net prevalence in both of inhalant allergens such as *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* and Graminaceae.

A strong patch test reaction is, in order of importance, the 3rd risk factor for LLAPTR (odds ratio 2.5). The data reported in the literature on this topic is scanty and conflicting. No correlation between the initial grade of positivity to nickel sulfate and duration of the patch test reaction was observed by Handley et al. (3). In patients with patch tests positive to gold sodium thiosulfate, Bruze et al. (11) observed a longer duration for the most intense reactions. According to Bygum & Andersen (9), persistent reactions to the standard series seem to be more frequent in patients with multiple strong patch test reactions. In our experience, persistence as LLAPTR mostly involves (23 cases) subjects with only 1 patch test reaction and with the characteristics of a strong reaction. Interestingly, in cases with 2 or more concomitant strong patch test reactions, evolution as LLAPTR, when present (15 cases), mainly involves only 1

positive patch test reaction (9 cases). The development of some reactions as LLAPTR and of others as NRAPTR in the same subject, with an equal degree of intensity of the patch test positivity, seems to be an interesting aspect, although inexplicable in the light of current knowledge. Strong patch test reactions were explained by the patient's present or past history in 72% (66% for weak reactions) of the cases. The relative risk for the relevant reactions to evolve as LLAPTR was in our series $2.2\times$ higher than those with unexplained relevance.

Finally, the frequency of LLAPTR, like the mean duration of the patch test reactions, is not correlated either with sex or with age. As far as age is concerned, there was a slightly higher prevalence of LLAPTR in the >60 year age group and a greater mean duration of the patch reactions, but with differences that were not statistically different with respect to the other age groups. Our results differ from those reported by Bassioukas et al. (12) relative to a significantly greater duration of the patch test reactions in older subjects (>60 years). According to the authors (12), the alterations in the cutaneous microcirculatory system in the elderly could lead to a reduced dermal clearance of the allergen with a consequent greater duration of the patch test reactions. This hypothesis, although attractive, is not confirmed by the data in our study.

In summary, our observations show a high frequency of LLAPTR. In a logistic regression model, Kathon CG sensitivity, atopy and strong patch test positivity proved to be significant risk factors for LLAPTR. The possibility that the same etiological factors behind LLAPTR are involved in determining many forms of chronic eczema (2) indicates the need for extensive further research into the subject.

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Address:

Giuseppe Mancuso
Via Pescantini 33
48022 Lugo (RA)
Italy