Acta Dermatovenerol Croat 2017;25(3):238-244 REVIEW

Long Lasting Allergic Patch Test Reactions: A Literature Review

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Received: February 29, 2016
Accepted: March 15, 2017

ABSTRACT Long-lasting allergic patch test reactions (LLAPTR) are those in which the clinical features of palpable erythema are still present at the site of a positive allergic patch test reaction 14 or more days after application of the allergen. LLAPTR have been described for a wide range of contact allergens, many of these included in the baseline patch test series. LLAPTR are far from uncommon; they occur in consecutive patients with positive patch tests to baseline allergens with frequency up to 17.9% of the total reactions. Patch test reactions persisting for a very long time (up to several months after the test) have been described, the most frequent ones being those induced by gold salts. The pathomechanisms of LLAPTR have not been clarified, but may hypothetically involve a constant antigen stimulation and/or a defect in cell-mediated immunity down-regulation. Host-related factors significantly associated with LLAPTR are, according to some studies, a strong initial patch test response, older age, and atopy. No significant sex differences have been observed in the frequency of LLAPTR.

KEY WORDS: long lasting allergic patch test reactions, baseline patch test series, gold salts, constant antigen stimulation, defective down-regulation of the immune response

INTRODUCTION

Long-lasting allergic patch test reactions (LLAPTR) are positive reactions at days 2-7 that remain positive for two weeks or more after application of the allergen (1). LLAPTR must be differentiated from late patch test reactions, i.e. those that become positive at day 7 or later (2). These do not necessarily indicate active patch-test sensitization and may indicate delayed expression of a pre-existing sensitivity (2). Traditionally, a late patch test reaction on day 10-14, which on subsequent retesting appears in the normal time schedule on days 2-4, is indicative of active sensitization from patch testing (3).

Frequency

The regular recall of positive patch test patients has demonstrated that LLAPTR are a more common event than previously recognized (4). In our previous study (5), LLAPTR occurred in 17.9% of the total reactions observed in consecutive patients with positive patch tests to baseline allergens, a value slightly higher than those reported by Bygum and Andsersen (6) and Alderdice *et al.* (7), 17% and 14.3%, respectively. Patch test reactions persisting for a very long time (up to several months after the test) have been described, the most frequent ones being those induced by gold salts (4,8). Long-lasting patch reactions to gold sodium thiosulfate (GST) frequently occur in patients with eczema as well as in healthy volunteers (8). In the study by Andersen and Jensen, 8 of the 31 (26%) healthy volunteers developed long-lasting patch test reactions to GST (8). However, the allergic nature of these positive reactions to gold was often questioned. The major argument for such questioning was the lack of demonstrable clinical relevance in most positive reactors (8).

LLAPTR-inducing allergens in reported case studies

LLAPTR are described for a wide range of contact allergens (1,4-28) (Table 1). Many of these are included in the baseline patch test series (5,6).

In earlier reports, persistent reactions have been reported from patch tests using gold chloride and gold sodium thiomalate (9), but not GST. For this reason, as well as for its lack of irritancy, GST has been suggested as a more reliable patch test substance for gold allergy (10). However, it has recently been observed that even GST may cause persistent patch test reactions (8,11-15).

In our two described cases, phenylephrine hydrochloride, a topical mydriatic agent for ophthalmic use, induced persistent (up to 5 and 7 months) and clinically relevant patch test reactions (16). Three subsequent cases of LLAPTR to phenylephrine hydrochloride have been reported (17-19).

Isaksson *et al*. observed that many patch test reactions to 2-hydroxyethyl methacrylate (2-HEMA) and ethyleneglycol dimethacrylate (EGDMA) persisted up to 28 days (20). Double active sensitization to EGDMA and 2-HEMA and active sensitization to camphoroquinone with LLAPTR in the same patient were previously reported by Malanin (21).

Corazza *et al*. described a case of allergic contact stomatitis from methyl methacrylate in a dental prosthesis, with a 30-day patch test persistent reaction (22). Sheehan and Zemtsov reported a case of clinically relevant LLAPTR to methyl methacrylate with a persistence of approximately 12 months (23).

In 11 patients wearing amalgam, restoration fillings and gold crowns, and presenting oral lichenoid contact lesions, Koch and Bahmer reported persistent patch test reactions to inorganic (12 cases) and organic mercury derivatives (6 cases), in addition to other allergens (25).

In a patient with atopic dermatitis described by Patrizi *et al*., patch tests with a textile series gave 6 positive reactions, only 2 of which (to Disperse Yellow 3 and Disperse Blue 35) evolved as LLAPTR (26).

Other LLAPTR-inducing allergens are reported in Table 1.

Clinical features

The morphological features of LLAPTR consist of palpable erythema, often associated with local itching and hyperpigmentation (6). These patch test responses frequently show clinical relevance and initial features consistent with a strong allergic patch test reaction (a ++ or greater reaction, according to the standard ICDRG criteria) (5,6,16-19,23-25,27,28). The relative risk for the clinically relevant reactions to evolve as LLAPTR was, in our baseline series of allergens, 2.2 times higher than for those with unexplained relevance (5). Two or more LLAPTR caused by separate allergens are sometimes seen in the same subject (5,6,20,21,25,26).

Histology

The histology of LLAPTR is characterized by a moderate to strong dermal lymphocytic infiltrate (band-like or perivascular), mostly with only slight epidermal changes (4). In some cases of LLAPTR to GST, the lymphocytic infiltrate was admixed with epithelioid-like cells with a tendency to granulomatous tissue reaction (12) or revealed a pseudolymphomatous structure with no significant epidermal eczematous changes (8,12). Persisting allergic patch test reaction to minoxidil, manifested as cutaneous lymphoid hyperplasia, was observed by García-Rodiño *et al*. (28). A lichenoid reaction pattern was present in 4 skin biopsies of persistent patch test reactions to inorganic mercury derivatives (25). No significant differences in the immunocytochemical nature of the localized immune reaction were observed between LLAPTR and the initial stages of allergic patch test reactions (4).

Underlying pathomechanisms

The pathomechanisms of LLAPTR have not been clarified, but may hypothetically involve a constant antigen stimulation and/or a defect in cell-mediated immunity down-regulation (4).

Constant antigen stimulation

Hypothetically, certain allergens, such as gold (29) and nickel (30), or their immunogenic degradation/metabolic products which persist in the skin for long periods of time, are able to produce constant antigen stimulation (4). It has been suggested that trivalent gold ions (as the reactive metabolite generated by mononuclear phagocytes from monovalent gold) may alter the presentation of self-proteins or alter the major histocompatibility complex molecules themselves. This may induce a persistent local immune reaction with graft-versus-host-like features (13).

Constant antigen stimulation could also be due to systemic exposure to contact allergens. Gold exposure at sites distant from the patch test site, for example jewelry and dental and intravascular implants, could through a systemic route play some role in the persistence of test reactions (31). Long-lasting reactions favored by systemic exposure to medical devices, jewelry, and other cutaneous applications as

Acta Dermatovenerol Croat
2017;25(3):238-244

Table 1. Long-lasting allergic patch test reactions (LLAPTR) in reported case studies

Responsible allergens	No. cases of LLAPTR in ( )	Notes in ( )
METALS		
Gold salts	8 (8); 2 (9); 1 (11); 10 (12); 3 (13); 1 (14); 1 (15)	Persistent reactions were induced by gold chloride and aurothiomalate in (9) and by GST in (8,11-15). A longer duration for the strong and early reaction to GST in patients tested with dilution series was observed in (12). An association between the strength of the initial patch test reaction to GST and its persistence was not present in (8). 11 different allergens gave LLAPTR, 8 a single such reaction, with nickel sulfate, potassium dichromate and colophony being represented 2X in 103 consecutive patients with positive patch test to baseline allergen series in (6)
Nickel sulfate	6 (1); 15 (5); 2 (6); 8 (30)	
Cobalt chloride	1 (6)	
Potassium dichromate	3 (4); 1(5); 2(6); 1 (25)	
Mercury derivatives	18 (25)	
Palladium chloride	2 (25)	
TOPICAL DRUGS		
Phenylephrine	2 (16); 1 (17);1 (18); 1 (19)	Systemic allergic contact dermatitis due to phenylephrine in eye drops was associated with a LLAPTR in (19)
Neomycin	2 (1)	
Gentamycin	1 (1)	Persistent patch test reaction to minoxidil mimicking pseudolymphoma was described in (28)
Minoxidil	1 (28)	
DYES		
PFD	1 (24); 1 (5); 1 (4)	LLAPTR to PFD was associated with a flare of previous ACD in (24)
Disperse Yellow 3	1 (26)	
Disperse Blue 35	1 (26)	
Disperse Blue 124	1 (5)	
PRESERVATIVES		
Thimerosal	1 (6)	
MCI/MI	16 (5); 1 (6)	MCI/MI was the most frequently LLAPTR-inducing allergen in a consecutive patient series with positive patch test to baseline allergens in (5)
Quaternium 15	1 (6)	
Formaldehyde	1 (6); 1 (1)	
ACRYILIC MONOMERS		
Methyl methacrylate	1 (22); 1 (23)	A longer duration for the strong and early reaction to 2-HEMA and EGDMA in patients tested with dilution series was observed in (20).
2-HEMA	1 (21); 11 (20)	
EGDMA	1 (21); 10 (20)	
RESINS		
PTBP-F-R	1 (6); 1 (25)	
Balsam of Peru	2 (1)	
Colophony	2 (1); 2 (6)	
PLANTS		
Parthenium hysterophorus	1 (27)	*Parthenium hysterophorus*, a plant belonging to the Compositae family. The open patch test evolved as a persistent reaction for up to 9 months (27)
RUBBER		
Thiuram mix	3 (1);1 (6)	
EXCIPIENTS		
Wool alcohols	2 (1)	
FRAGRANCE MIX	1 (1); 1 (4); 1 (6)	
OTHER SUBSTANCES		
Camphoroquinone	1 (21)	Camphoroquinone, a visible-light photoinitiator

References in parentheses: ( ); ACD: allergic contact dermatitis; MCI/MI: methylchloroisothiazolinone/methylisothiazolinone in a 3:1 ratio; HEMA: 2-hydroxyethyl methacrylate; EGDMA: ethyleneglycol dimethacrylate; GST: gold sodium thiosulfate; PTBP-F-R: p-tert-butylphenol-formaldehyde resin; PFD: p-phenylenediamine.

well as from hidden oral intake cannot be excluded for ubiquitous allergens such as chromium, cobalt, and nickel (32). Significantly, flares of previous patch test reactions to nickel have been reported after oral challenge (33).

There are no recent literature data evaluating the local immune response associated with prolonged antigen stimulation in LLAPTR. Notably, a shift from typical Th1- to Th2-type cytokine reactivity observed upon prolonged contact allergen exposure (34,35) represents a possible event in LLAPTR. There are no experimental data that may confirm this possibility.

A defective down-regulation of the immune response

Resolution of allergic contact dermatitis was initially attributed to clearance of the allergen. However, recent studies have demonstrated the long-term persistence of the allergen in the skin of the contact reaction for some experimental antigens, such as fluorescein isothiocyanate, despite resolution of symptoms (36). Today, it appears evident that numerous regulatory mechanisms suppress or limit the inflammation to avoid tissue damage. These mechanisms may involve, among others:

- The elimination of antigen-loaded dendritic cells (37);

- Non-MHC ligand production for inhibitory immune receptors (38);

- Down-regulation of adhesion molecules E- and P-selectins on endothelial cells (39);

- Activation of regulatory lymphocytes or mast cells with IL10-induced immunosuppressive functions (40,41).

In addition, the inflammatory response is actively down-regulated by CD4+ T- (Treg) cells during the resolution phase (34,36). The mechanisms by which Treg cells limit the immune reaction have not been clarified yet and may involve IL10 and other immunosuppressive cytokines (34,42-45).

Studies have so far failed to identify a defect of one or more immunoregulatory mechanisms as a possible cause of LLAPTR. It has been suggested that HLA-DR keratinocytes generate down-regulatory signals to terminate immunologically induced cutaneous inflammation. However, Todd *et al*. did not find any significant difference in keratinocyte expression of HLA-DR, DP, and DQ antigens between LLAPTR and normally resolving patch test reactions (NRAPTR) to various baseline patch test allergens (1). A subsequent study on LLAPTR and NRAPTR to nickel by Handley *et al*. confirmed the observations by Todd *et al*. (30).

Interestingly, in cases with two or more concomitant patch test reactions to separate allergens with the same initial intensity (++ or +++) in the same subject, evolution as LLAPTR, when present, mainly involves some of these reactions (5,25,26). The evolution of some reactions as LLAPTR and of others as NRAPTR seems to be a very inexplicable aspect, if we consider the general defect of the immunoregulatory mechanisms as the one and only responsible. The co-existence of other local factors, and in particular of factors linked to the allergen or to its metabolites able to interfere with the host immune response in that individual, seems highly likely.

Other factors associated with LLAPTR

The strength of initial patch test reactions

Contrasting data have been reported on the relationship between the strength of initial patch test reactions and LLAPTR. According to Bygum and Andersen (6), LLAPTR to the baseline series allergens seem to be more frequent in patients with multiple strong patch test reactions. In patients with patch tests positive to GST, Bruze *et al*. observed a longer duration for the strong and early reactions (12). No correlation between the initial grade of positivity to nickel sulfate and duration of the patch test reaction was observed by Handley *et al*. (30).

Age

As far as age is concerned, Bassioukas *et al*. (46) demonstrated a significantly greater duration of the patch test reactions in older subjects (>60 years). According to the authors, the changes 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 previous study (5).

Sex

No significant sex differences have been observed in the frequency of LLAPTR (5).

Atopy

In our study, the risk for LLAPTR was significantly greater in atopic than in non-atopic individuals (5).

A proinflammatory cytokine milieu in atopic dermatitis (predominance of Th2 in acute and Th1 cytokines-IFN-γ in chronic lesions) may act as a danger signal and facilitate contact allergy response (47). However, the influence of atopy on the course of patch test reaction remains to be determined. Interactions

favoring the persistence of the contact allergic reaction could occur at multiple levels: increased survival of inflammatory cells in allergic tissues (47,48); incessant production of large amounts of chemotactic and proinflammatory mediators by preactivated dendritic cells and persistent activation of pathogenic lymphocytes (47,49); a reduced number or defective function of regulatory T-cells and related cytokines (IL10 and TGF-β) (47,50); endogeneous corticosteroid resistance (51,52).

CONCLUSION

The very limited and at times contrasting data do not provide a clear and satisfactory explanation of the pathomechanisms underlying LLAPTR. The possibility that the same pathomechanisms are involved in determining many forms of chronic eczema indicates the need for extensive further studies on this issue.

Acknowledgements

The author thanks Alessandra Mancuso for critical reading of the manuscript.

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