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Case Report

Significance of Late Phase Reaction in Allergy Skin Testing in Polysensitized Patients-A Case Series

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Abstract

There are no systematically documented studies on Late Phase Reaction (LPR) and isolated late phase reaction (ILPR) in medical literature. LPR is an IgE mediated sequalae to the early immediate reaction of type I and type IV (b) hypersensitivity reaction of Gell & Coomb's classification. We describe, three cases of respiratory allergy with perennial symptoms and seasonal exacerbation, co-morbid with Oral Allergy Syndrome (OAS) (case 1), Rhino-sinusitis (case 2), and Hypothalamus-pituitary Adrenal (HPA) suppression (case 3), polysensitized to various groups of allergens. In our three cases, polysensitization could be a compounding factor due to pan-allergens or tropomyosin. Component Resolved diagnosis (CRD) by specific IgE can identify clinically significant allergens when immediate reaction by skin test and specific IgE of allergen extract fail to reveal the true sensitization. We hypothesize in our three cases that Dual Phase Reaction (DPR) [Immediate reaction (IR) and LPR] should be considered to differentiate between genuine species-specific relevant sensitization from cross-reactive sensitization till facilities for CRD are available.

Keywords: Late Phase Reaction (LPR); Immediate Reaction (IR); Dual Phase Reaction (DPR); Isolated Late Phase Reaction (ILPR); Allergen Immunotherapy (AIT); House dust mite, Cockroach; Cyanodon dactylon; Skin Prick Test (SPT); Oral Allergy Syndrome (OAS); Hypothalamic Pituitary Adrenal (HPA) suppression; Component Resolved diagnosis (CRD)

Introduction

The clinical relevance of late phase reaction (LPR) has not been thoroughly studied. LPR signifies the late allergic bronchial inflammation indirectly, equivalent to the challenge test. Whether it differentiates genuine species-specific sensitization from cross-reactive sensitization, needs further studies. It is important to remember that the distinction between IR and LPR is based arbitrarily on IR with 20% fall in FEV1 or a 50 % fall in specific airway conductance within 15 minutes. While, LPR is based on 20% fall in FEV1, 3 to 12 hours after a challenge test [1].

When LPR was originally described, it was thought that the mechanism might be a type III reaction (immune complex-mediated) due to precipitating IgG antibody. However, precipitating antibodies have not been found with LPR. Later, research confirmed that the LPR is an IgE-depenent sequalae to the Immediate Reaction (IR), on-going eosinophilic inflammation along with mast cell-derived arachidonic acid metabolites [2,3]. The frequency of LPR varies in different reports from 33 to 73%.

Green and colleagues studied delayed reactions after 48 hours and observed that 5% of all skin tests had isolated late phase reaction (ILPR) at 48 hours and 13% of skin test sites with positive IR also showed delayed reactions (IR + LPR) at 48 hours [4]. ILPR has no IR (wheal and flare) and no symptoms of itching at skin site and can develop in the same time frame (appears in 3-4 hours and peaks at 6-8 hours after skin tests).

LPR is defined as an area of oedema and erythema of at least 5 mm diameter, present 3-6 hours following an IR after testing at a skin test site. The immediate wheal and flare reaction develops within a minute after the skin test [(Skin Prick Test (SPT)/Intradermal Skin Test (IDST)], peaks at about 15 minutes and resolves in 30-60 minutes. The oedema and erythema of LPR begins after 1 hour, peaks at 3-6 hours and is sustained for 6-8 hours, resolving by 24-48 hours (Figure 1). Both IR & LPR are continuous during evolution of inflammation of immediate (Wheal & Flare) & late Phase reactions (Edema & Erythema) [5]. Histological studies of the dual phase skin reaction (DPR) reveals that, IR is characterized by vasodilation and oedema of the

papillary dermis due to histamine while the LPR is characterized by a mixed cellular infiltrate of eosinophils, monocytes, lymphocytes and basophils [3]. Usually, bigger wheal size of IR is followed by an LPR. LPR is an IgE mediated sequalae of Type-I, followed by Type-IV(b) hypersensitivity reaction of Gell and Coomb's classification having mast-cell derived arachidonic acid and eosinophilic metabolites along with cellular inflammation. Mast cell degranulation initiates a complex sequence of immunological events resulting in a DPR (IR+LPR) and other mast cell generated mediators such as leukotrienes C4, B4, D4, prostaglandin D2 and/or platelet activating factor, can be detected in the skin during the LPR development. Histamine does not cause LPRs and anti-histamines do not block the development of the LPR [6]. Polysensitization is defined as sensitivity to multiple allergenic molecules leading to production of specific IgE antibodies of various specificities regardless of symptoms (Figure 2). While cross-reactivity describes the situation when multiple sensitivities are consequences of reactivity of the same species-specific IgE antibodies with antigenic structure of homologous allergen molecules from different allergen sources. According to Calderon et al, 50-80% of patients with allergic diseases are polysensitized and 60% of which are sensitized to grass pollen and house dust mite (HDM) [1,7]. Kathuria et al., also observed polysensitization in 80% of subjects [8]. HDM (Dermatophagoides pteronyssinus-Dp / Dermatophagoides farinae-Df), grass pollen (Cyanodon dactylon, Pennisetum notatum), Tree pollen (Holoptelea intergrifolia, Prosopis juliflora, Ricinus communis), weed pollen (Artemesia vulgaris, Amaranthus spinosus, Argemone Mexicana), Cockroach and Moulds (Alternaria alternata, Cladosporium, Aspergillus fumigatus) are the most common allergens prevalent in India [9].

In patients of polysensitization, Component Resolved Diagnosis (CRD) helps us to distinguish between sensitization to species-specific allergens and cross-reactive allergens. The IR (wheal and flare) was read at 15 minutes and interpretated as positive; 1+, 2+, 3+, 4+ in accordance with the recommended criteria of the Scandinavian society of allergology. The LPR (oedema and erythema) was read at 2 hours, 3 hours, 6 hours and graded as; Grade I- less than 10 mm (1cm), grade II- 10 to 20 mm (1-2 cm), grade III-20 to 30 mm (2-3 cm) and grade IV- more than 30 mm (>3 cm) [10]. We report three cases of respiratory allergy with perennial symptoms and seasonal exacerbation, co-morbid with Oral Allergy Syndrome (OAS) (case 1), Rhino-sinusitis (case 2), and Hypothalamic pituitary adrenal (HPA) axis suppression (case 3), polysensitized to various groups of allergens. SPT was done using standardized allergen extracts and was found to be significantly positive with IR (wheal and flare) and LPR (oedema and erythema) to Cyanodon dactylon (case 1), cockroach (case 2) and HDM (Dp / Df) [case 3]. Specific IgE concentration was measured by ImmunoCap. In all three cases, there was a correlation between the wheal size in IR (>5mm) and LPR (>10 mm) with specific IgE (>1.0 kUA). We hypothesize that if CRD facilities are unavailable and IR by SPT fails to reveal the true clinically relevant allergen then, LPR with specific IgE titre of allergen extract and patient's clinical history is enough to identify the clinically relevant allergens. All our three cases were given single allergen immunotherapy, which was safe, effective, having a long lasting effect.

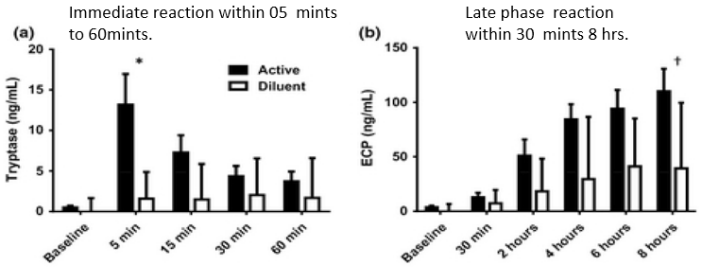


Figure 1: Immediate and Late phase reaction.

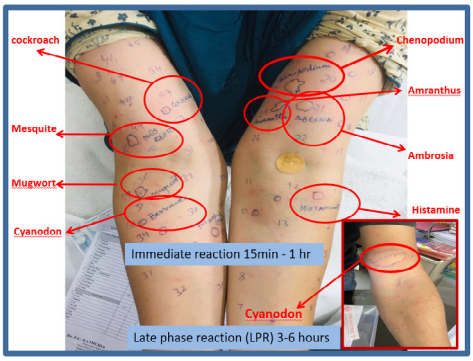


Figure 2: IR and LPR in a polysensitized patient.

Case presentation

Case 1

55 years old female presented with history of respiratory allergy with perennial symptoms and seasonal exacerbation, co-morbid with OAS. In-vivo and In-vitro testing- Blood investigations revealed (Table 1): Total IgE was elevated- 605 IU/ml. SPT-IR (wheal and flare) were positive for Timothy grass (Phleum pretense)-8mm, Orchard grass (Dactylis glomerata)-8mm, Rye grass (Lolium perenne)-8mm, Bermuda grass (Cynodon dactylon: IR-9 mm, LPR-13mm), Velvet grass (Holcus lanatus)-8mm, Johnson grass (Sorghum halapense), corn (Zea mays)- 6mm, Pennisetum-9mm, Peanut-6mm, Wheat flour-6mm, Corn flour-6mm. After waiting for 3 hours, we found significantly positive LPR (oedema and erythema)-13mm (grade 2), only to Cyanodon dactylon while rest of the allergens waned and disappeared after an hour. Serum specific IgE was positive for Bermuda grass (Cynodon dactylon)->100 Kua/L, Wheat- 11.1 Kua/l, Peanut8.87 kUA/l. OFC positive to chia seeds.

Recommendation: Cynodon Allergen Immunotherapy (AIT) and Inj Omalizumab with diet elimination. Symptoms gradually improved.

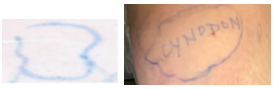
	Case 1	
Total IgE	605 IU/ml	
	SPT wheal size / Oedema size	Specific IgE
Histamine	6mm 	N/A
Cynodon dactylon	**IR- 9mm** **LPR- 13mm**  <1 hour >3 hours	>100 kUA/L
Pennisetum notatum	9mm 	ND
Peanut	6mm 	8.87 kUA/L
Wheat	6mm 	11.1 kUA/L
Corn	6mm 	N/A

Table 1: In-vivo and In-vitro testing- Blood investigations revealed.

Case 2

13 years old male, case of respiratory allergy, chronic rhino-sinusitis with perennial symptoms and seasonal exacerbation (Nov-Jan). Symptoms exacerbate on exposure to cockroach at home and are more during the night. He was prescribed Long-acting beta agonist (LABA), Inhaled corticosteroids (ICS) with on and off intake of Oral corticosteroid oral (OCS) and anti-histamines but had no relief. *In-vivo and In-vitro test*: Total IgE-247 IU/ml. SPT-IR (wheal and flare) were positive for **Cockroach: IR-8mm / LPR-11 mm,** Dp - 5mm, Df- 5mm, Fish- < 3mm. After waiting for 3 hours, we found significantly positive LPR (oedema and erythema)-11mm (grade 2) only to cockroach while Dp and Df waned and disappeared after an hour. *Specific IgE* were positive for **Cockroach-9.47 Kua/L** and negative for Dp- <0.1 Kua/l, Df- <0.1 Kua/l and Fish- <0.1 Kua/L (Table 2).

Recommendation: Cockroach AIT with effective dose was prescribed along with pest-control measures. Achieved remission.

	Case 2	
Total IgE	247.0 IU/ML	
	SPT wheal size/ Oedema size	Specific IgE
Histamine	 5mm	N/A
Cockroach	**IR-8mm** **LPR-11 mm**  **<1 hour** **>3 hours**	9.47 kua/l
D. pteronyssinus	5mm	<0.1 kua/l
D. farinae	 5mm	<0.1 kua/l

Table 2: Clinical characteristics of case 2.

Case 3

16 years old female, history of respiratory allergy with perennial symptoms and seasonal exacerbation, sneezing and wheezing during house-cleaning associated with HPA suppression since 6-7 years. She took symptomatic and indigenous treatment (on & off OCS) with poor relief. In-vivo and In-vitro test: Total IgE-2597 IU/ml. SPT-IR (wheal and flare) were positive for Dp / Df: IR- 10mm/ LPR-12mm, Cockroach-7mm, Chenopodium album- 4mm, Pennisetum notatum-5mm, Prosopis juliflora-4mm, Cynodon dactylon-4mm, Ricinus communis-4mm. After waiting for 3 hours, we found significantly positive LPR (oedema and erythema)-12mm (Grade 2), only to DP and DF. Specific IgE were positive for Dp- >100 Kua/l, Df- 93.30 Kua/l, Cockroach-11.20 Kua/l. (Table 3).

Recommendation- HDM AIT was given for two years, achieved remission.

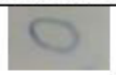
	CASE 3	
Total IgE	2597 IU/ML	
	SPT wheal size / Oedema size	**Specific IgE**
Histamine	 5mm	N/A
D. pteronyssinus	**IR-10mm** **LPR-12mm**   <1 hour >3 hours	>100.0 kua/l
D. farinae	 10mm	93.30 kua/l
Cockroach	 7mm	11.20 kua/l

Table 3: clinical characteristics of case 3.

Discussion

Polysensitization is a risk factor for severity of diseases and for subsequent development of allergic asthma. The prevalence of polysensitization increases with age with 54% in children under 11 years, 61.7% in adolescence and 64.8% in adults ($p<0.001$) in French odyssey study [11]. Older guidelines do not recommend AIT for polysensitized patients [10]. AIT is a relative contraindication in polysensitized patients as per AIT practice parameter, third update. It emphasized the selection of relevant allergens for AIT but none of the guidelines however, gives pragmatic recommendations to identify the relevant allergens during skin tests. When considering the composition of AIT formulations, the GA2LEN/ EAACI guidelines do not recommend mixtures for multi-AIT. Real life observation and post marketing studies show that AIT is safe and effective in polysensitized patients and it does not influence the indication for AIT. Our key task is to establish, which of the sensitized allergens are relevant with regard to the clinical symptoms of allergy. SPT wheal diameter and specific IgE of allergen extract have limited value in identifying clinically relevant species-specific allergens in polysensitization. Allergen challenge (for eg., nasal challenge, conjunctival challenge, or exposure in a challenge chamber) is difficult to perform. CRD may help to distinguish between genuine clinical sensitization and cross-sensitization, but facilities are not available. One has to differentiate which of the positive allergens are clinically dominant relevant allergens, maybe one or only a couple of them. When a positive allergen does not cause symptoms, AIT is not indicated. AIT in polysensitized patients will be ineffective and may lead to deterioration of symptoms if relevant species-specific allergens are not included in the allergen vaccine.

We hypothesize, that patient's clinical history correlating with both, IR and LPR after allergy skin testing and specific IgE data is sufficient to identify genuine clinical sensitization and cross-sensitization. Our three cases were given AIT after considering both IR and LPR rather than IR alone. Polysensitization was not an obstacle for AIT. We found that single allergen immunotherapy was successful in treating our 3 polysensitized cases of respiratory allergy with perennial symptoms and seasonal exacerbation, co-morbid with OAS (case 1), Rhino-sinusitis (case 2), and HPA suppression (case 3). In case 1 Cyanodon dactylon was selected

for AIT because it was significantly positive (IR and LPR) and has limited cross-reactivity. In case 2, cockroach allergen, even though poorly standardized was considered because of clinical correlation and positive IR and LPR. In case 3, HDM (DP/DF) had a strong correlation with clinical history and positive IR + LPR. Unfortunately, there are no systemically documented studies on IR and LPR in allergy skin testing in medical literature. Occurrence of LPRs after allergen skin testing has not been thoroughly studied, further investigation is required to evaluate the clinical relevance of LPRs.

Conclusion

CRD may help to distinguish between genuine clinical sensitization and cross-sensitization, but facilities are not available. IR and LPR together are immunologically more significant and have a shown a promising role in differentiating between clinically relevant and irrelevant sensitization. The occurrence of LPR following IR after skin testing is not a biphasic reaction rather a continuous inflammatory process. The medical literature has little information regarding late phase reaction to allergy skin testing. Selection of the clinically relevant allergen should be based on both IR and LPR rather than on IR alone. Polysensitization is not an obstacle for AIT. Further studies are needed to evaluate the clinical relevance of Late Phase reaction (LPR) in polysensitized patients.

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