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Original Article

Clinical and Immunological Correlates of Skin Prick Test Reactivity and Anaphylaxis during Allergen-Specific Immunotherapy in Children with Asthma and Allergic Rhinitis

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Abstract

Background: Allergen-specific immunotherapy (AIT) is an effective treatment for allergic rhinitis and asthma, aiming to induce immune tolerance through repeated exposure to allergens. Although skin prick testing (SPT) is commonly used to identify sensitized individuals, its predictive value for systemic reactions during AIT, including anaphylaxis, remains uncertain. To investigate the correlation between the diameter of the wheal in SPT and the incidence of anaphylactic shock during subcutaneous immunotherapy in patients with allergic rhinitis and asthma.

Methods: This cross-sectional observational study included 255 pediatric patients aged 3–18 years with allergic rhinitis and/or asthma who underwent SPT at an allergy clinic in 2019. Patients with a positive SPT (wheal ≥3 mm) received subcutaneous AIT using standard allergen extracts for a period of three years. All patients were monitored for 20 minutes post-injection for adverse reactions. The size of SPT wheals was compared between patients who experienced anaphylactic reactions and those who did not.

Results: The mean age of patients was 10.2 ± 3.7 years; 68.2% were male. Of the 255 patients, 2.4% (n=6) experienced anaphylactic shock—two of grade I and four of grade II severity. Anaphylaxis occurred only in patients with allergic rhinitis or rhinitis combined with asthma; no cases were observed in patients with asthma alone (p=0.04). The average SPT wheal sizes for common allergens, particularly Dermatophagoides pteronyssinus, were slightly larger in patients with anaphylaxis, but the differences were not statistically significant (p>0.05).

Conclusion: There was no significant correlation between SPT wheal size and the risk or severity of anaphylaxis during AIT. However, allergic rhinitis appeared to be more associated with systemic reactions than asthma. These findings suggest that the magnitude of local skin reactivity may not reliably predict systemic hypersensitivity outcomes during immunotherapy. Further studies with larger sample sizes and more advanced immunological profiling are recommended.

Keywords: Skin Prick Test; Anaphylaxis; Subcutaneous Immunotherapy; Allergic Rhinitis; Asthma; IgE; Pediatric Allergy

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Introduction

Allergic diseases, including allergic rhinitis and asthma, are among the most prevalent chronic disorders in children worldwide, with rising incidence rates in both developed and developing countries (1,2). The emergence of these conditions is mainly via an amplified immune response to environmental allergens that are generally harmless, such as pollen, dust mites, animal dander, and mold spores. The immunopathogenesis of allergic rhinitis and asthma involves immunoglobulin E (IgE)-mediated hypersensitivity reactions. In these reactions, allergen-specific IgE antibodies bind to high-affinity FcεRI receptors on the surface of mast cells and basophils, triggering degranulation and the release of mediators such as histamine, prostaglandins, leukotrienes, and other pro-inflammatory substances. (3,4)

Allergic rhinitis is a chronic inflammatory disorder of the nasal mucosa, often accompanied by sneezing, nasal congestion, rhinorrhea, and pruritus of the nose, resulting in reduced quality of life and school performance among children. (5) In addition, allergic rhinitis is now known to be a major risk factor for the future development of asthma. (6) Asthma is a chronic inflammatory disease of the airways characterized by variable and reversible airflow obstruction, bronchial hyperresponsiveness, and airway remodeling that is often precipitated or exacerbated by exposure to allergens. (7) Several T cell subsets, including Th2, Th17, and regulatory T cells (Tregs), are now recognized to contribute to the immunopathology of asthma above and beyond the classical Th2 paradigm. (8,9)

Although pharmacological therapies, such as corticosteroids and β2-agonists, help alleviate symptoms, they are not intended to correct the immune dysregulation. Allergen-specific immunotherapy (AIT), and subcutaneous immunotherapy (SCIT) in particular, is the only therapeutic option that alters the disease progression by teaching the individual long-term immune tolerance through repeated exposure to increasing doses of allergens (10). AIT has been shown to reduce symptoms and medication use, as well as decrease not only the risk of new sensitizations but also the likelihood of progression to asthma from rhinitis (12,13).

The skin prick test (SPT) is commonly used to identify allergen sensitization and estimate IgE threshold reactivity through wheal-and-flare responses caused by the local degranulation of mast cells in a sensitized patient (14). The overall diameter of the wheal reaction is considered a semi-quantitative approximation of the allergen-specific IgE compared to eliciting a flare reaction (15). However, the correlation between the size of the wheal and the systemic reaction during AIT, including anaphylaxis, remains unclear. Anaphylaxis, although infrequent, is the most serious adverse effect associated with SCIT and requires careful monitoring with risk stratification to reduce the likelihood of elicitation (16). Some studies have reported a high serum-specific IgE as a risk factor (17,18), but they have either not examined the semi-quantitative measure of the SPT wheal as a predictor of anaphylaxis or the measure of severity to predict the risk of reaction. Therefore, this study aims to evaluate the correlation between the size of SPT wheals and the incidence and severity of anaphylaxis during SCIT in children with allergic rhinitis and/or asthma. A better understanding of this association may contribute to improved risk assessment and safety in clinical immunotherapy protocols.

Materials and Methods

Study Design and Participants

This observational cross-sectional investigation took place at the Allergy Clinic located in Bushehr, Iran, between March and December 2019. The study included forty-five pediatric patients, aged from 3 to 18 years, who were diagnosed with allergic rhinitis and/or asthma and expressed willingness to participate following a preliminary clinical examination. All subjects were referred for SCIT following standard diagnostic and therapeutic criteria.

Study eligibility criteria comprised children aged 3–18 years with a confirmed diagnosis of allergic rhinitis classified as moderate to severe and/or asthma classified as mild to moderate persistent according to the Global Initiative for Asthma (GINA) and Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, and all patients had tested positive with a SPT, defined as a wheal diameter at least 3 mm larger than the diameter of the negative control. Patients were excluded

if they had severe persistent asthma, suffered a history of anaphylaxis unrelated to SCIT, or had other medical conditions, including cardiovascular disease, chronic pulmonary disease other than asthma, immunodeficiency, autoimmune disorders, and psychiatric comorbidities. Additionally, those who had taken any non-steroidal anti-inflammatory drugs (NSAIDs) within 72 hours preceding testing or had mild or intermittent allergic rhinitis were deemed ineligible.

Skin Prick Testing (SPT)

SPTs were performed on the volar surface of the forearm, utilizing a standardized allergen extract (Greer® Laboratories, USA). The SPT panel included the most prevalent inhalant allergens, such as house dust mite (Dermatophagoides pteronyssinus), and generated pollen from grasses, trees, and weeds (ragweed and mugwort), as well as Salsola kali (Russian thistle). For SPTs, each patient was pricked with a sterile lancet through a small drop of allergen extract. Reactions were read after approximately 15 minutes. A positive SPT was defined as a mean wheal diameter ≥3 mm larger than the negative control (saline), and histamine control was used as a positive control.

Immunotherapy Protocol

All patients with a positive SPT underwent a three-year program of SCIT. The SCIT protocol was followed as a classical buildup and then maintenance schedule, as per Middleton's recommended guidelines. The allergen extracts were administered SC on a weekly basis during the buildup phase (lasting approximately 12-16 weeks) to achieve the recommended maintenance dose. The maintenance phase consisted of SC injections every four weeks, with the allergen dose adjusted according to each patient's individual clinical response and tolerance. Each patient received approximately 40 injections over the entire course of therapy. A pediatric resident with education in allergy management and additional supervision performed all immunotherapy procedures. Following each injection, patients were observed in the clinic for at least 20 minutes to monitor potential local or systemic adverse reactions.

Monitoring for Adverse Reactions

All systemic side effects were identified, classified according to the World Allergy Organization (WAO) classification system, and graded for severity. A grade I reaction included urticaria, flushing, and/or angioedema; grade II occurred with gastrointestinal or respiratory symptoms and tachycardia; grade III included bronchospasm, laryngeal edema, and/or cyanosis; and grade IV cardiac or respiratory arrest. Systemic events occurring within 30 minutes of supervised SCIT administration were recorded as adverse events. Patients were assessed for 1 year after treatment was initiated, and any events that occurred were recorded in the patient's chart.

Data Collection and Variables

Demographic data (age, sex), clinical diagnosis (asthma, rhinitis, and/or both), duration of allergic disease, and wheal diameters from skin prick tests at baseline were recorded. Systemic side effects, including anaphylaxis, were documented while receiving immunotherapy. The primary outcome was the frequency and severity of anaphylactic reactions, measured against SPT wheal size and type of allergen.

Statistical Analysis

Data were analyzed using SPSS version 24 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Independent sample t-tests and ANOVA were used to compare means across groups. Categorical data were analyzed using Chi-square or Fisher's exact test where appropriate. A logistic regression model was used to evaluate the association between SPT wheal size and the occurrence of anaphylaxis. A p-value <0.05 was considered statistically significant.

Ethical Considerations

Informed consent was obtained from the legal guardians of all participants. The study protocol was reviewed and approved by the Ethics Committee of Bushehr University of Medical Sciences. All procedures were conducted in accordance with the Declaration of Helsinki.

Results

A total of 255 pediatric patients with allergic rhinitis and/or asthma were included in the

study. The mean age was 10.2 ± 3.7 years (range 3–18 years), with 68.2% (n=174) males and 31.8% (n=81) females. The distribution of underlying allergic diseases included 35.7% (n=91) with asthma, 25.9% (n=66) with allergic rhinitis, and 38.4% (n=98) with both conditions. The mean duration of allergic disease was 61.6 ± 40.6 months **(Table 1)**.

Among all patients, 3.5% (n=9) experienced systemic side effects, including urticaria (0.8%), eczema (1.6%), and unspecified adverse effects (1.2%) **(Table 2)**.

Anaphylaxis occurred in 2.4% (n=6) of patients: 0.8% had grade I and 1.6% had grade II reactions. All cases occurred within 20 minutes post-injection **(Table 3)**.

No anaphylactic events were observed in patients with asthma alone (p=0.04) **(Table 4)**. Although mean wheal diameters were slightly larger in patients with anaphylaxis for dust mite and Salsola allergens, no statistically significant differences were observed ($p > 0.05$) **(Table 5)**.

Table 1. Demographic Characteristics of Patients

Variable	Value	Percentage (%)
Total patients	255	100
Male	174	68.2
Female	81	31.8
Asthma	91	35.7
Allergic rhinitis	66	25.9
Asthma + Rhinitis	98	38.4
Mean age (years)	10.2 ± 3.7	-
Mean disease duration (months)	61.6 ± 40.6	-

Table 2. Frequency of Systemic Reactions during Immunotherapy

Type of Reaction	Number of Cases	Percentage (%)
Urticaria	2	0.8
Eczema	4	1.6
Unspecified	3	1.2
No systemic reaction	246	96.5

Table 3. Incidence and Severity of Anaphylaxis

Grade of Anaphylaxis	Number of Cases	Percentage (%)
Grade I	2	0.8
Grade II	4	1.6
Total	6	2.4

Table 4. Anaphylaxis by Type of Underlying Disease

Underlying Disease	Anaphylaxis Cases (n=6)	Percentage (%)
Allergic Rhinitis	4	66.7
Asthma + Rhinitis	2	33.3
Asthma alone	0	0

As illustrated in **Figure 1**, the mean wheal diameters were slightly larger in patients who experienced anaphylaxis compared with those who did not, particularly for Dermatophagoides pteronyssinus and Salsola kali. However, these differences were not statistically significant ($p > 0.05$), indicating that the extent of skin reactivity in SPT does not reliably predict systemic hypersensitivity

during allergen-specific immunotherapy.

The distribution of underlying allergic diseases among participants is presented in **Figure 2**, showing that the majority of patients had both asthma and allergic rhinitis, followed by isolated asthma and rhinitis cases.

Discussion

This investigation examined the clinical and immunological correlation between SPT wheal

Table 5. Mean Wheal Diameter by Allergen and Anaphylaxis Status

Allergen	With Anaphylaxis (Mean ± SD)	Without Anaphylaxis (Mean ± SD)	*p*-value
Dust Mite	8.0 ± 6.7	6.8 ± 3.9	0.50
Grass	7.0 ± 3.6	6.3 ± 3.8	0.70
Tree	5.0 ± 0.0	5.0 ± 2.9	0.90
Weed	3.0 ± 0.9	6.9 ± 4.2	0.13
Salsola	7.3 ± 6.4	9.3 ± 5.2	0.40

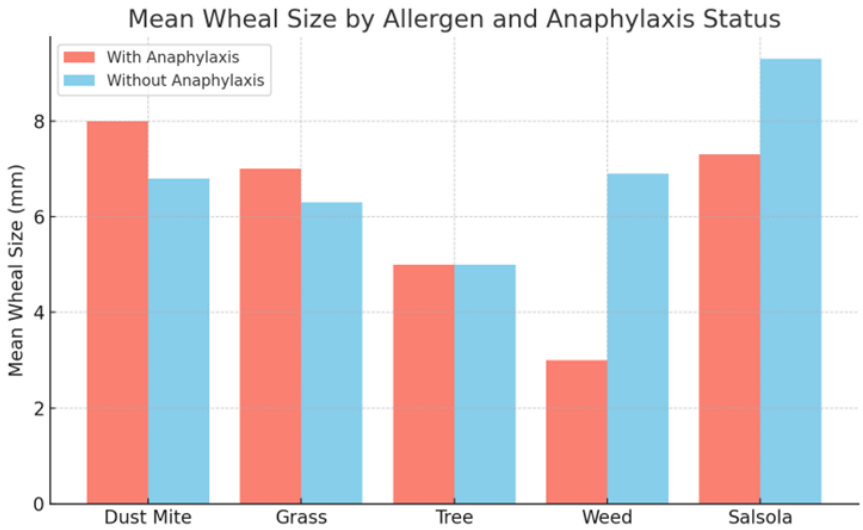

Figure 1. Comparison of mean wheal diameters (in mm) between patients with and without anaphylactic reactions across five allergens.

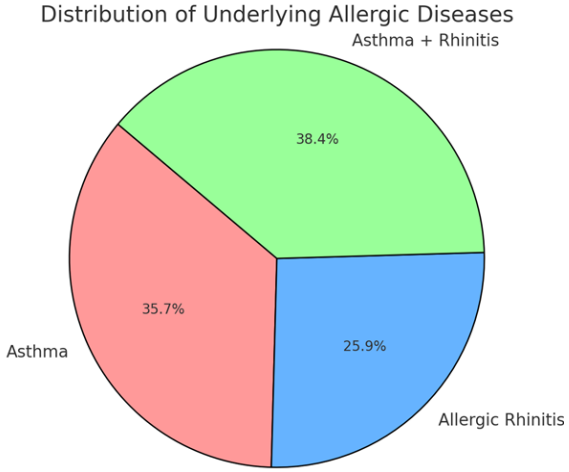

Figure 2. Distribution of Underlying Allergic Diseases

size and the risk of anaphylaxis during SCIT in a group of pediatric patients with characterized allergic rhinitis and/or asthma. While patients who had anaphylaxis had slightly larger mean wheal diameters—particularly for Dermatophagoides pteronyssinus and Salsola kali—these differences did not reach statistical significance. This indicates that the size of the cutaneous IgE-mediated reactivity is not a reliable indicator of systemic hypersensitivity risk during SCIT.

The overall incidence of systemic reactions (3.5%) and anaphylaxis (2.4%) observed in our study was consistent with previously reported rates of 3–7% for systemic reactions associated with SCIT using standardized allergen extracts (17,19). Interestingly, all patients who experienced anaphylactic reactions only had a history of allergic rhinitis or allergic rhinitis with asthma. There were no observations of anaphylaxis in patients diagnosed solely with asthma. This may be explained by airway mucosal mast cell reactivity since the upper airway (oro-nasal mucosa) is believed to have more mast cells than the lower airway (which is primarily IgE mediated) (4,7). These observations lead us to suggest that patients with a history of allergic rhinitis may be more predisposed to mast cell involvement for systemic activation during immunotherapy courses.

While earlier studies have created associations between elevated serum allergen-specific IgE and an increased risk of systemic reactions (17,18), SPT wheal size serves as only a surrogate marker for overall sensitization, and it has demonstrated limited correlation with in vitro IgE measurements (15). Furthermore, the wheal reflects local cutaneous mast cell activity, which may not fully represent systemic immune reactivity once the patient begins to develop tolerance through immunotherapy (10,11). The absence of correlation between wheal size and anaphylaxis in our cohort corroborates this distinction and is in harmony with parallel findings in pediatric population samples reported by Heinzerling *et al.* (19) and most recently, by Kim *et al*, who established that the SPT wheal size did not predict systemic adverse events during SCIT in a Korean pediatric population (20). SCIT works through a myriad of immunomodulatory mechanisms, including the induction of allergen-specific IgG4, T regulatory cell expansion, and the suppression of Th2-mediated inflammation (8,9,10). These processes alter systemic immune responsiveness, making local skin test reactivity an insufficient biomarker of therapeutic safety. Our staggered dose build-up, compliance with WAO safety guidelines, and 20-minute observation period post-injection accounted for the low percentage of severe reactions and no grade III-IV reactions (16). The greatest strength of this study was the systematic documentation of adverse events in a homogenous pediatric population, and it provided stratified analyses by disease type and allergen. Limitations to our study include a single-center design and the lack of confirmatory laboratory markers such as serum-specific IgE, IgG4 levels, or basophil activation testing. Future multicenter trials incorporating these immunologic assays, as well as longitudinal monitoring of immunological tolerance markers, would help refine risk prediction models and improve clinical decision-making.

Conclusion

Our findings indicate that SPT wheal size does not significantly correlate with the risk of anaphylaxis during SCIT in children. Clinicians should be cautious in interpreting large wheal reactions as indicators of increased systemic risk. Instead, a comprehensive approach involving patient phenotype, disease severity, and rigorous dosing protocols remains essential to ensuring immunotherapy safety. Particular attention should be paid to patients with allergic rhinitis, who may have an inherently higher susceptibility to systemic reactions.

Conflict of interest

There is no conflict of interest.

Acknowledgment

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