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The Superiority of Intradermal Testing in the Diagnosis of Allergic Diseases

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Abstract

The purpose of this study was to determine the sensitivity advantage of intradermal dilutional testing (IDT) in the diagnosis of allergy in patients with various atopic diseases such as chronic sinusitis, allergic rhinitis, asthma or otitis media with effusion. This retrospective, private-practice cohort study compared the sensitivity of skin prick tests (SPT) vs. IDT in 110 adults and children with suspected allergy. This retrospective, private-practice cohort study compared the sensitivity of SPT vs. IDT in 110 adults and children with suspected allergy. Primary outcome measure was symptom resolution from allergy immunotherapy (AIT). IDT identified 57% more patients as being allergic, and 8.6 times more reactive allergens than would have been diagnosed using only Skin Prick Testing (SPT). IDT identified 57% more patients as being allergic, and 8.6 times more reactive allergens than would have been diagnosed using only SPT. Patients diagnosed by IDT had the same degree of symptom improvement from immunotherapy, independent of allergen sensitivity (66% by SPT vs. 63% by IDT; p = 0.69, not different). Low-sensitivity allergy tests, which may fail to identify allergy in over two thirds of children aged 3 to 15 as being a topic, or among 60% of patients with middle ear disease, may explain why many physicians do not consider allergy as a treatable etiology for their patient's allergies. IDT offers superior sensitivity over SPT for detecting allergens clinically relevant to treating allergy. These data strongly support increased utilization of intradermal testing and invite additional clinical outcome studies.

Keywords: Eustachian Tube Dysfunction; Otitis Media; Skin Prick Test; Asthma; Allergic Rhinitis; Allergy Testing; Allergy Immunotherapy; Intradermal Test

Abbreviations

SPT: Skin Prick Tests, IDT: Intradermal Dilutional Tests, AIT: Allergy Immunotherapy.

Introduction

Allergy tests detect hypersensitivity to allergens suspected of triggering symptoms, but are all skin tests equivalent in their responses? Skin prick tests (SPT) are often the only tests used to diagnose allergy, because intradermal dilutional tests (IDT) are thought by some to offer no additional relevant information and are more time consuming.[1]. However, the subsequent decision to treat with allergy immunotherapy (AIT), and the resulting therapeutic response, depend on the ability of the chosen test to identify truly allergic individuals and their significant allergens [2]. Yet, physicians face a conundrum in diagnosing patients with classic signs and

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symptoms of allergy when SPT are negative.

This study was designed to determine whether the difference in sensitivity between IDT and SPT is clinically relevant in patients with asthma or allergic rhinitis, or otitis media with effusion (OME). We compared the AIT responses of low-sensitivity patients who were identified only by IDT, that is, those who have had negative results with SPT and those showing positive results with IDT; i.e., low-sensitivity (SPT−/IDT+) vs. high-sensitivity patients (SPT+).

Relationship of Allergy to ETD

Current best evidence supports an association between allergic rhinitis (AR) and eustachian tube dysfunction {ETD). Meta-analysis suggests a strong correlation between AR and OME among children [3]. Yet, not all patients with ETD suffer from AR, and vice versa [4]. Exposure to allergen challenge has consistently resulted in a dose-dependent decrease in ET patency, regardless of whether a seasonal (ragweed) or perennial (dust mite) allergen challenge was used [5]. Evaluation of the records of 2.4 billion pediatric visits found allergy to be associated with a 2- to 4.5-fold increased incidence of OME [6].

Many OME clinical studies over the past 75 years have shown both an increased association of allergy symptoms (rhinitis, asthma, and eczema) and positive in vivo or in vitro tests for IgE [7].

Some clinicians feel that low-sensitivity allergy detected by IDT is not clinically meaningful, citing concerns that low-sensitivity patients require more concentrated antigen for testing which can result in false positives [1].

We believe that the results of many prior studies, which are dependent on the sensitivity of the type of allergy test used, have underestimated the true incidence of allergy among atopic patients by using tests with poor sensitivity. This study was designed to test the hypothesis: IDT, compared to SPT, has greater sensitivity for detecting allergens that are clinically relevant in patients with asthma and allergic rhinitis. Our test of hypothesis was by evaluation of each patient's AIT response, as reflected in his or her perceived symptom improvement.

ETD, asthma, and AR were diagnosed based on clinical symptoms, compatible physical findings, and positive skin tests [8] Ethics approval was obtained from the Diagnostics 2021, 11, 763

Franklin Memorial Hospital Committee on Ethics and Human Experimentation (Farming- ton, ME 04938, USA, Personal letter June 2006). Informed consent for allergy testing was obtained from the patient or parent for both testing and treatment.

Materials and Methods

This is a retrospective study of 110 patients in a solo, community-based practice who presented with chronic (≥3 months) symptoms or signs of obstructive ETD that meet the criteria as defined in a Clinical Consensus Statement [9]. Assessments included history, otologic exam, and pneumatic otoscopy. Asthma, and AR were diagnosed based on clinical symptoms, compatible physical findings, and positive skin tests [10].

Allergy Testing

All patients were tested by the primary author using multi-dilution IDT according to current practice parameters [11,12] for Dermatophagoides pteronyssinus, Dermatophagoides farinae, cat, dog, American cockroach (Periplaneta Americana), grass (timothy or meadow fescue), tree (birch or oak), ragweed, goldenrod, lambs quarters, Alternaria alternata, and Cephalosporium acremonium.

Patients were tested with 4mm intradermal wheals [13] and with glycerin-matched control tests [14]. IDT test allergens were serially diluted five-fold, six times, from standardized extracts or the highest concentration available, usually 1:20 w/v (Greer, Lenoir, NC 28633, USA). Testing was begun at dilute allergen concentrations with Dilution 5 (D5); 1:62,500 w/v or Dilution 4 (D4); 1:12,500 w/v; and continuing up to the most concentrated dilution tested (D2), 1:500 w/v. Intracutaneous tests of wheal growth were measured 10 to 15 min after injection and both wheal and erythema (in millimeters) were recorded. Positive test or "end point" was defined as the lowest concentration of allergen that produces a wheal: (1) that the first wheal is 2 mm larger than the negative control wheal and (2) is followed by a second wheal that is at least 2 mm larger than the preceding one. Patients who were completely negative for all skin tests were not offered immunotherapy and were excluded from the study, as were those with craniofacial abnormalities, muscular dystrophy, history of previous cholesteatoma, autoimmune disorder, or those who only had in-vitro testing.

Thirty-nine patients had SPT performed by AAAAI board certified physicians within two years prior to enrollment. Records of these skin tests were obtained. These patients were re-tested by IDT and are included in this study.

Subgroup A patients reacted to allergens only on the strongest concentration tested, D2 (1:500 w/v). Subgroup B reacted to one allergen at D3 (1:2500 w/v) and all others to dilution D2. Subgroup C reacted to more than one allergen at

D3 and the rest at D2. Subgroup D reacted to a single allergen at D4 (1:12,500 w/v), with all other positive allergens identified at stronger concentrations. Subgroup E were the most sensitive, reacting to at least two allergens at dilution D4 or weaker.

Skin Test Responses: A = all D2 (1:500 w/v), B = D2 and 1 D3 (1:2500 w/v), C = D2 and D3, D = at least 1 D4 (1:12,500 w/v), and E = 2 or more D4. Percent improvement is: (pretreatment symptom score minus symptom score after AIT)/pretreatment symptom score.

SPT Status

Positive IDT dilution results were categorized as being high-sensitivity reactors (SPT+/IDT+) or low-sensitivity reactors (SPT−/IDT+) using the known sensitivity of the Multi-test II (Lincoln Diagnostics, Decatur, IL 62526, USA) as being between IDT D3 (1:2500 w/v) and D4 (1:12,500 w/v).

Relative Allergen Sensitivity

Patients were sorted based on their relative allergen sensitivity. The average number of identified allergens per person, gender, and age in each subgroup was compared in the table under results.

Immunotherapy

Patients with positive skin tests were offered AIT if their allergy symptoms were not adequately controlled by medications and avoidance, or if they wished to reduce medications. AIT was provided for all IDT positive allergens.

Patient-Reported Symptom Score

The primary outcome was the patient's reported symptom score. Improvement among children was based on their parent's report of symptom relief and diminution of episodes of recurrent OME. A 10-point forced-choice Likert-type questionnaire was administered pre-treatment and after achieving AIT maintenance.

Results

One hundred ten patients met inclusion criteria for the study. Patient ages ranged from 3 to 70 years (59 females, mean 35.3 years, 51 males, mean 25.3 years). Fifty-three (48%) were children 3 to 15 years old, of whom 72% were SPT negative.

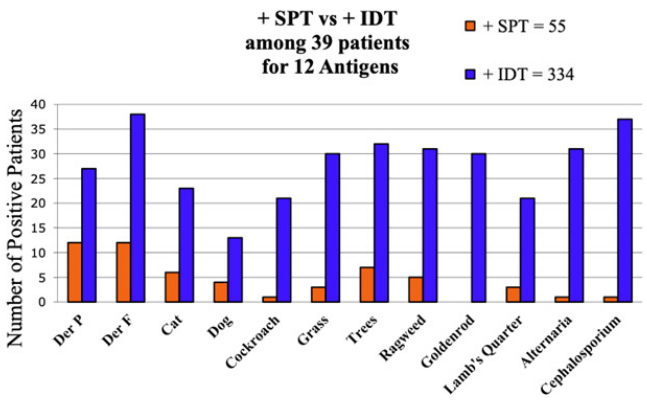

Figure 1: Comparisons of allergen detection by both SPT and IDT. Number of positive skin-test reactions by SPT and IDT to each of 12 allergens among 39 patients tested by both methods.

Direct Comparison of SPT and IDT

There were 39 patients initially tested by certified allergists using only SPT and subsequently retested by us using IDT. Comparing tests for the same 12 allergens, SPT was found to detect only 16% of allergens found by IDT (Figure 1).

The two tests agreed as positive in 78 (20%) and negative in 88 (22%). IDT differed from SPT among 231 (58%) antigen tests as it detected 3.8 times more allergens (total of 334 vs. 55) per patient than SPT (9.5 vs. 2.5, $p < 0.01$). SPT exhibited a sensitivity of 16% of that of IDT, using IDT as the standard. Only 8% of initial SPT wheals were positive and based on those tests AIT had been offered by the allergists to merely 8 (20.5%) patients. In contrast, IDT found all 39 to be allergic. AIT was recommended to all 39.

Allergy Testing Effectiveness of IDT

Skin testing in the 110 patients was positive for 833 of 1320 allergy tests placed. Forty-seven (43%) high-sensitivity (SPT+) patients were positive for only 81 allergens. IDT

identified 305, or 3.8 times, additional treatable allergens among these high-sensitivity SPT+ patients (subgroups D&E) than did SPT alone (81) (Chi-Square $p < 0.001$, 95% CI: −0.47, −0.36), (odds ratio 0.09; 95% CI: 0.05 to 0.15).

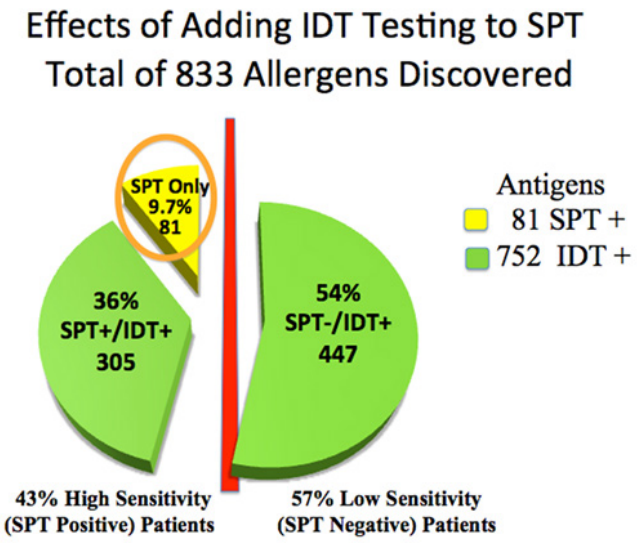

Figure 2: Advantage of adding IDT testing to SPT: total allergens discovered. Circled: 81 antigens positive by SPT.

Identifying these allergens may have improved the chances of including all relevant allergens for AIT. IDT was significantly more sensitive than SPT (Chi-Square $p < 0.001$, 95% CI: −0.47, −0.36).

Sixty-three low-sensitivity (SPT−) patients were positive only by IDT among low-sensitivity IDT+ (subgroups A, B, and C. Table 2, Figure 2), identifying an additional low-sensitivity IDT+ (subgroups A, B, and C. Table 2, Figure 2), identifying an additional 447 potentially treatable allergens. These 63, 57% of all patients, would have been incorrectly identified as non-allergic by relying only on SPT.

Children are especially likely to be missed if IDT is not done: 38 (72%) of the 53 children ages 3–15 expressed low sensitivity: SPT−/IDT+ (subgroups A, B, and C). Of these, 30 (83%) were in the lowest sensitivity subgroup A. This demonstrates the necessity of testing children with the most concentrated dilution, 1:500 w/v, in order to diagnose allergy in young OME patients.

Response to AIT Is Independent of Skin Sensitivity

Pre-treatment and post-treatment symptom scores, and percent improvement for each group after reaching AIT maintenance, were recorded. In the SPT+ high-sensitivity group (subgroups D, E) the average pre-treatment symptom scores were reduced from 8.13 to 2.75 (66% improvement). In the low-sensitivity IDT+ group (subgroups A, B, C), the average pre-treatment symptom scores were reduced from 8.51 to 2.95 (63% improvement). The difference proved to be not significant (Chi Sq $p = 0.86$ = NS; 95% Cl: −0.048, 0.040),

AIT Results Unaffected by Co-morbid Allergic Diagnoses

We found 81% had two or more allergic diagnoses, including 79 (72%) with AR and 39 (35%) who had asthma. Improvement was statistically not different for the total of study patients with co-morbid allergic diagnoses of AR plus asthma (63%, $p = 0.98$ = NS).

Duration of AIT Benefit

Sixty-eight patients, previously reported, with OME/ETD or retracted tympanic membranes and who had either type B or C tympanograms [11], underwent a subgroup analysis. Sixteen of 17 type B returned to type A, while all 19 type C returned to normal following AIT. Fifty-five patients completely and five partially resolved their ETD following AIT, maintaining resolution for four to seven years of follow-up. Of the 441 antigens detected among those who resolved, only 40 (9%) would have been detected by SPT.

Discussion

The purpose of this study was to demonstrate that the sensitivity of the skin testing method used to diagnose allergy. The difference in expected outcome for adults has been demonstrated previously. Among the children ages 4–15, complete resolution was experienced by 92%, whereas only 83% of those 16–50 and only 46% of those 51–70

experienced complete resolution after AIT [11].

In order to resolve a patient's OME, it is essential to identify that the patient is allergic. Clearly no matter how they were tested, once they were identified as allergic, immunotherapy was effective in more than half of patients reported from 1942 to 2008.

Conclusion

The data from these 110 patients strongly supports our hypothesis: IDT demonstrated a markedly greater sensitivity for detecting allergens that are clinically relevant for AIT than did SPT. Use of only SPT in our patients would have failed to identify 57% of individuals as having allergic disease, including 72% of children ages 3–15 who were SPT negative. Adding IDT following negative SPT doubled the number of patients diagnosed as being allergic (Figure 2) and almost tripled the number of children. Use of only SPT would also have missed 91% of IDT positive antigens that might have been critical to successful AIT treatment

Institutional Review Board Statement

Ethics approval was from the Franklin Memorial Hospital (Farmington, Maine) Committee on Human Experimentation.

Informed Consent Statement

Written informed consent was obtained from all subjects or their parents for allergy testing and treatment involved in the study.

Data Availability Statement

The data presented in this study are available on request from the corresponding author, David Hurst. The data are not publicly available due to privacy of patient identity.

Acknowledgments

Statistics were calculated by Abou El-Makarim Aboueissa, Ph.D., Professor of Statistics, Department of Mathematics and Statistics, University of Southern Maine, using SAS 9.4 software (SAS® Institute Inc., Cary, NC 27513, USA). Statistics consisted of T test and Chi Sq testing to distinguish any statistical difference between groups. Thanks to Melissa A. Weekley, MD for reviewing this manuscript.

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