Patch Testing in an Allergy Clinic: Real-world Experience

Shira Rosenberg-Bezalel MD, Daniel Elbirt MD, and Keren Mahlab-Guri MD

Department of Clinical Immunology Allergy and AIDS, Kaplan Medical Center, Rehovot, Israel

ABSTRACT **Background:** Contact dermatitis is an inflammatory skin disorder characterized by an erythematous pruritic rash. The disorder can be either irritant or allergic. Allergic contact dermatitis is diagnosed by patch testing along with patient history.

Objectives: To review the results of patch tests conducted thought 2 years and to present real-life data characterizing clinical features and comparing prevalent local allergens to the ones common worldwide.

Methods: The retrospective cohort included 517 participants (384 females and 133 males) who underwent patch testing during a 2-year period. For each patient, clinical and demographic data were collected, and statistical analysis was conducted.

Results: We found that 261 patients had a positive test for at least one allergen. More females tested positive than males (52.9% vs. 43.6%). Test indications other than dermatitis were associated with a negative result. Hands, head, and neck were the most prevalent body parts affected. Patients with a background of atopic dermatitis had a higher rate of contact sensitization (69 vs. 43). Patients with a specific suspected offending allergen had significantly higher contact sensitizations. The most common allergen was nickel.

Conclusions: Patch testing should be conducted in patients with relevant dermatological findings accompanied by taking a thorough medical history. Clinicians should be updated on emerging allergens and exposure trends.

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KEY WORDS: allergic contact dermatitis, dermatitis, patch test

Contact dermatitis is a common inflammatory skin disease encountered by allergists, dermatologists, and primary care physicians. The disease is characterized by an erythematous pruritic rash, which may present in an acute, subacute, or a chronic manner [1]. Disease prevalence is estimated to be 4.17% in the United States [2]. Contact dermatitis can be either irritant or allergic. Irritant contact dermatitis is a result of cumulative exposure to weak irritants and accounts for the majority of the cases of contact dermatitis. In contrast, allergic contact dermatitis (ACD) is the result of a delayed hypersensitivity immune reaction (T cell mediated) to a specific allergen. ACD represents 20% of the cases of contact dermatitis [3].

Patient evaluation begins with a thorough history taking in search for exposure to a potential allergen. The gold standard for diagnosing ACD is patch testing [4]. The specific test should be relevant to the patient's possible exposures and test results should be validated as relevant or not. Trends in allergic exposure are constantly evolving. The importance of different allergens as potential sensitizers varies through time depending on usage extent [5].

In this study we reviewed the results of patch tests performed in our allergy unit during 2 years. The objectives were to present real-life data, to characterize clinical and demographic features of patients with ACD, and to compare the local common allergens to the frequent allergens worldwide.

PATIENTS AND METHODS

The study was a retrospective cohort study. Patients included those who underwent patch testing between September 2016 and August 2018 at the department of clinical immunology allergy in the Kaplan medical center, Rehovot. The study was approved by the Kaplan Medical Center ethics committee.

The study included 517 patients. For each participant, epidemiological and clinical data were collected. Epidemiological information included: sex, age at time of testing, and occupation. Clinical data collected referred to the following: test indication, body part affected, presence of atopic dermatitis (AD), presence of a specific suspected substance, and the particular patch testing preformed. Test results were recorded as positive or negative according to the International Contact Dermatitis Research Group [1]. Positive allergens were specified. The relevancy of the tests results to patient condition was assessed.

Patients were tested using the European baseline series and/or a variety of international series manufactured by Chemotechnique Diagnostics (Sweden). These Patch Test Haptens are authorized by the International Contact Dermatitis Research Group (ICDRG). The allergens were loaded onto IQ ULTRATM patch test units. In a small number of patients the test was conducted using personal products loaded onto the same chambers. According to guidelines, evaluation took place 48 and 72 hours after test application [1].

STATISTICAL ANALYSIS

The categorical variables are presented as mean ± standard deviation. Comparison between two categorical variables (posi-

tive/negative) was conducted using Pearson chi-square tests. Continuous data were compared using Shapiro-Wilk test. When abnormal distribution was found, the Mann-Whitney test was performed. *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

The study group consisted of 384 females and 133 males with an average age of 42.9 ± 19 years. There were no significant differences in age among patients with a positive test and patients with a negative test. Of the 384 females tested, 203 (52.9%) had a positive test. From the 133 males tested, 58 (43.6%) were positive. This difference did not reach statistical significance ($P = 0.06$). There were 114 patients (22%) who tested positive to one allergen, 85 (16.4%) had two positive allergens, and 29 (5.6%) were positive to three allergens. Table 1 outlines the number of positive allergens per patient.

The most frequent indication for conducting patch testing was dermatitis, 61.3% of the 282 patients who were tested due to dermatitis had a positive patch test with $P < 0.001$. A significantly higher rate of negative patch tests was seen among patients tested due to pruritus ($P = 0.01$), rash ($P = 0.008$), urticaria ($P = 0.009$), and a group of skin diseases including dyshidrosis, seborrhea, and psoriasis ($P = 0.006$). A high percentage of positive tests was observed among patients tested due to ophthalmic complaints (66%) and atopic dermatitis exacerbation (75%); yet, these results did not reach statistical significance ($P = 0.32$ and $P = 0.32$, respectively) probably due to the small numbers. Table 2 presents the indications for the tests conducted with regard to the test outcome.

The most prevalent body parts affected were the hands, and second were the head and neck. Yet, none of the body parts affected had a statistically significant correlation with a positive test. Patients with disseminated complaints had a higher rate of negative tests, which reached statistical significance, $P = 0.03$.

Data regarding AD were available for 160 patients. Of 91 patients with a negative history for atopic dermatitis, 43 (47%) had a positive patch test. Forty of the 69 (57%) patients with a background of atopic dermatitis had a positive patch test. The difference did not reach statistical significance, $P = 0.17$.

We found that 115 patients had a specific suspected material as a cause of their symptoms, in contrast to 402 patients who did not suspect a particular allergen. The rate of positive tests among the group with a suspected deleterious allergen was 63.5%, in contrast to 46.7% positive tests in patients without a specific suspect. This difference was statistically significant, $P = 0.002$.

A total of 717 tests were conducted. These tests included a wide variety of commercial available patch tests and personal products. The most prevalent test conducted was the baseline European series, which presented 65.5% of the tests conducted. The series used in this study are detailed in Table 3.

The most prevalent allergen was nickel, which tested positive in 105 patients. Fragrance mix 1 was positive in 48 patients and Methylisothiazolinone/methylchloroisothazolinone was positive in 43 patients. Table 4 lists the frequent positive allergens in descending order.

Of 261 patients with a positive patch test, 109 patients had a clear history of exposure to the offending allergen or allergens. The most prevalent allergens with an explicit clinical relevance were as follows: nickel (40 patients), fragrances, and Peru balsam (22 patients), paraphenylendiamine (PPD) (15 patients), methylisothiazolinone/methylchloroisothazolinone (14 patients), acrylates and nails (11 patients), cobalt (9 patients) and paraben mix (6 patients).

Table 1. Number of positive tests per patient

Number of positive tests	Number of patients
0	256 (49.5%)
1	114 (22%)
2	85 (16.4%)
3	29 (5.6%)
4	15 (2.9%)
5	6 (1.1%)
6	5 (0.9%)
> 6	7 (0.3%)

DISCUSSION

We characterized features of patients with allergic contact dermatitis. A positive test was more likely among females. Patients presenting with dermatitis had a higher rate of positive tests in contrast to patients with a main complaint of pruritus, rash, and other skin conditions. Disease affecting hands, face, and neck were more prevalent in patients with proven ACD (without statistical significance); however, a disseminated disease was negatively associated with a positive patch test. Patients with ophthalmic complaints or AD exacerbation had a high rate of positive tests without statistical significance. We did not prove a correlation between a background of AD and increased probability of ACD. A significant higher rate of positive patch tests was observed among patients presenting with a specific suspected allergen.

The European baseline series was the most common test conducted, and the most frequent positive tests were for nickel, followed by fragrance mix-1 and methylisothiazolinone/methylchloroisothazolinone.

Table 2. Test indication

Test indication	Number of patients	Positive test	Negative test	*P* value
Dermatitis	282	173 (61.3%)	109 (38.7%)	< 0.000
Pruritus	96	38 (39.6%)	58 (60.4%)	0.018
Oral-dental	16	9 (56.3%)	7 (43.8%)	0.639
Rash	49	16 (32.7%)	33 (67.35)	0.009
Atopic dermatitis deterioration	4	3 (75%)	1 (25%)	0.325
Ophthalmic	9	6 (66.7%)	3 (33.3%)	0.327
Urticaria	10	1 (10%)	9 (90%)	0.009
Dyshidrosis, seborrhea, psoriasis	14	2 (14.2%)	12 (85.8%)	0.006
Drugs	3	1 (33.3%)	2 (66.7%)	0.556
Other	34	12 (35.2%)	22 (64.8%)	0.067

Table 3. The test performed

Tests preformed	Number
Personal products	15 (2.0%)
Standard	470 (65.5%)
Cosmetics	90 (12.5%)
Nail + Acrylates	29 (4.0%)
Dental	26 (3.6%)
Textile	20 (2.7%)
Hair dye	17 (2.3%)
Metals	14 (1.9%)
oils	12 (1.6%)
Shoe	7 (0.9%)
Fragrance	6 (0.8%)
Sun screens	5 (0.6%)
Drugs	5 (0.6%)
Epoxy	1 (0.1%)
Total	717

Table 4. Frequent positive allergens

Allergen	Positive results
Nickel	105
Fragrance mix 1	48
Methylisothiazolinone/ methylisothiazolinone + methylchloroisothiazolinone	43
Paraphenylenediamine + hair dyes	36
Cobalt	32
Peru balsam	23
Potassium dichromate	20
Acrylates	19
Thiuram mix	12
Paraben mix	11

A higher rate of allergic contact dermatitis among women has been described in a number of studies [6,7], especially in facial disease [8,9]. This phenomenon is generally related to different exposure patterns rather than to endogenous factors [10].

Generally, ACD clinical presentation includes a pruritic eczematous eruption in the acute phase and lichenification, scaly plaques, or fissuring in the chronic phase [11,12]. In the case of systemic contact dermatitis, an exposure to a known sensitizer may cause a flare at a previous coutaneous site of exposure or a generalized dermatitis [11,13]. Certain allergens, such as PPD, can cause a dramatic facial swelling that can be mistaken for a type I allergic reaction [12]. Nevertheless, dermatitis is the fundamental presentation of ACD, and presence of dermatitis is a basic requirement before proceeding to patch testing.

Previous studies addressed the issue of body sites affected in contact dermatitis. One study found the hands to be the most

frequent skin area affected [14]. Another study concluded the hand and the head to be the most common sites of ACD [15]. The anogenital region was the least frequent area affected with dermatitis [14]. Apart from the hands and head, the feet and eyelids and a unilateral presentation are highly suggestive for ACD [1].

In our study, a high percentage (66%) of the patients with ophthalmic complaints had a positive test. This result did not reach statistical significance due to the small numbers. When comparing patients with one or two sensitizations to patients with a polysensitization (three or more), dermatitis did not seem to be more wide spread [14]. The adverse correlation between a disseminated disease and a positive patch test is reasonable given that ACD is typically a limited skin condition.

Patients with atopic dermatitis have, theoretically, an increased risk for developing ACD. The allegedly increased risk is related to the impaired skin barrier with increased penetration of allergens, immune dysregulation, and frequent exposure to chemicals in topical products [16]. A met-analysis by Hamann et al. [17] revealed no significant association between AD and contact sensitization, yet patients with AD had a higher prevalence of contact sensitization in general population studies. Another systemic review by Simonsen and colleagues [18] assessing contact allergy in children with AD showed ACD to be more frequent in children without AD compared to children with AD. However, ACD is a common problem among children with AD, affecting approximately one third of these patients [16]. In the current study data regarding AD were available for only 30.1% of the participants. There was no significate difference in contact sensitization between patients with a positive background for AD and patients with a history negative for AD. Three of four patients tested due to AD deterioration had a positive test. This finding is consistent with the recommendation for patch testing AD patients with a suspected allergic contact dermatitis [17] or patch testing in cases that the AD is resistant to topical treatment [16].

A high percentage of positive patch tests were observed among patients with ophthalmic complaints (without statistical significance). The eyelids are considered to be a vulnerable skin area, significantly thinner than the rest of the facial skin, and susceptible to irritants and allergens [19].

Patients with a specific suspected culprit allergen had a significant higher rate of positive patch tests. Previous studies concluded that self-reported nickel allergy had a low validity [20,21]. Another study concluded that self-reported rashes caused by metals or jewelry had a positive predictive value of 50–70% and a higher negative predictive value [22]. Patients with a previous skin reaction to cosmetic products had significantly more positive patch tests reactions in a prior study [23]. It is a reasonable finding that a specific complaint yields a higher percentage of positive tests with a varying predictive value among the different allergens.

The top 10 most frequent positive allergens in the North American Contact Dermatitis Group (NACDG) patch test results for 2015–2016 were as follows: nickel, methylisothiazolinone, fragrance mix I, formaldehyde 2%, methylchloroisothiazolinone/methylisothiazolinone, moroxylon pereirae, neomycin, bacitracin, formaldehyde 1% and p-phenylendiamine [24]. Compared to the current study, five of the allergens were common, with four of them ranked closely. The similarities and differences represent common and distinct patterns of exposure in different countries. The prevalence of contact allergy to acrylates in the study represents the increasing trend of exposure and hence allergy to these substances [25]. 2-hydroxyethyl methacrylate (2-HEMA) 2% has been added to the European baseline series of 2021 as a marker for acrylate allergy.

STRENGTHS

The study was comprised of a large number of patients who were enrolled and included the availability of a wide range of patch test series to coordinate with patient complaints and exposures.

LIMITATIONS

Our study has several limitations. First, it is a retrospective study. Second, some of the information about occupational exposure was missing.This information could assist to evaluate the relevancy of the test results. Third, data of personal history of atopic dermatitis were available for less than half of the participants. This sparse information made it difficult to assess the impact of atopic dermatitis on allergic contact dermatitis in the study group.

CONCLUSIONS

When evaluating a patient with suspected contact allergy, taking a through history, proceeding with a patch test in patients with appropriate localized dermatological findings, updating on emerging allergens and exposures trends, and choosing the appropriate patch test series are important. We also recommend adding a later visit, after the patient has avoided exposure to the allergens that tested positive, to evaluate the relevancy of the results on patient health.

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Correspondence

Dr. S. Rosenberg-Bezalel
Dept. of Clinical Immunology Allergy and AIDS, Kaplan Medical Center, Rehovot 76100, Israel
Fax: (972-8) 941-0461
email: ros.shira@gmail.com

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If an animal does something, we call it instinct; if we do the same thing for the same reason, we call it intelligence.

Will Cuppy (1884–1949), American humorist and literary critic, known for his satirical books about nature and historical figures

Capsule

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Five patients (four women and one man) with systemic lupus erythematosus (SLE), median age of 22 years, median disease duration of 4 years, and active disease SLE disease activity index Systemic Lupus Erythematosus Disease Activity Index: 16 refractory to several immunosuppressive drug treatments, were enrolled in a compassionate-use chimeric antigen receptor (CAR) T cell program by **Mackensen** and co-authors. Autologous T cells from patients with SLE were transduced with a lentiviral anti-CD19 CAR vector, expanded, and reinfused at a dose of 1 × 10^6 CAR T cells per kg body weight into the patients after lymphodepletion with fludarabine and cyclophosphamide. CAR T cells expanded in vivo led to deep depletion of B cells. Improvement of clinical symptoms and normalization of laboratory parameters including seroconversion of anti-double-stranded DNA antibodies were shown. Remission of SLE according to DORIS criteria was achieved in all five patients after 3 months and the median Systemic Lupus Erythematosus Disease Activity Index score after 3 months was 0. Drug-free remission was maintained during longer follow-up (median of 8) months after CAR T cell administration) and even after the reappearance of B cells, which was observed after a mean of 110 ± 32 days after CAR T cell treatment. Reappearing B cells were naïve and showed non-class-switched B cell receptors. CAR T cell treatment was well tolerated with only mild cytokine-release syndrome. These data suggest that CD19 CAR T cell transfer is feasible, tolerable and highly effective in SLE.

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Eitan Israeli