Evaluation of the permanence of skin sensitization to allergens in patients with allergic contact dermatitis*

Avaliação da persistência de sensibilização a alérgenos em pacientes com diagnóstico de dermatite alérgica de contato

Ida Duarte[1]
Andrey Augusto Malvestiti[2]
Rosana Lazzarini[4]
Mariana de Figueiredo Silva[2]
Beatriz de Abreu Ribeiro Machado[3]

Abstract: BACKGROUND: Background: Patch tests are an efficient method to confirm the etiological diagnosis of allergic contact dermatitis.
OBJECTIVES: 1) To determine the permanence of results between two tests performed with an interval of at least one year, in patients with allergic contact dermatitis; 2) To compare the positive results according to rates of intensity; 3) To evaluate the permanence of sensitization according to each substance that was tested.
METHODS: Patients with previous diagnosis of allergic contact dermatitis, confirmed by patch tests carried out between the years 2005 and 2008, underwent new testing, using the same methodology, and data was compared.
RESULTS: A total of 1470 results of both tests on 49 patients were analyzed. The negative results remained in the second test in a rate of 96%, and 4% became positive (+) without relevance to the clinical history. Moreover, moderately (++) and strongly (+++) positive results were also maintained in, respectively, 86% and 100%. Nevertheless, weakly (+) positive results became negative in 65%. By ignoring all weakly (+) positive tests, the calculation of Kappa Index of Agreement Statistics between the two tests showed a value of 0.88.
CONCLUSION: Patch tests showed to be reliable for negative, moderately (++) positive and strongly (+++) positive results, by reproducing the same standard of individual response to allergens. However, for weakly (+) positive results, tests were not reliable.
Keywords: Dermatitis, allergic contact; Dermatitis, contact;Diagnosis; Patch tests; Skin tests

Resumo: FUNDAMENTOS: Testes de contato positivos, relevantes com a história clínica, identificam os materiais que desencadeiam a dermatite alérgica de contato (DAC).
OBJETIVOS: 1)Verificar a persistência ou não de resultados entre testes de contato realizados com intervalo mínimo de um ano, em pacientes com dermatite alérgica de contato; 2)Determinar a persistência de testes de contato positivos de acordo com a sua intensidade (+, ++ ou +++); 3)Avaliar a permanência de sensibilização de acordo com cada substância testada.
MÉTODO: Pacientes com diagnóstico prévio de DAC, confirmado por testes de contato realizados entre 2005 e 2008, foram submetidos à realização de novos testes, utilizando a mesma metodologia do anterior, e os dados foram comparados.
RESULTADOS: Um total de 1470 resultados dos dois testes realizados em 49 pacientes foi analisado. Os testes negativos mantiveram-se no segundo teste em 96% e 4% passaram a positivo (+), sem apresentar relevância com a história clínica. Nenhum teste negativo no primeiro teste passou para positivo de intensidade (++) ou (+++). Além disso, os testes positivos(++) mantiveram-se em 86% dos testes e, os positivos (+++), em 100%. Já em relação aos testes positivos(+), 65% tornaram-se negativos. Ao se desconsiderar todos os resultados positivos(+), o índice Kappa foi de 0,88, evidenciando concordância excelente entre os dois testes realizados.
CONCLUSÕES: Os testes de contato mostraram-se confiáveis para os resultados negativo, positivo (++) e (+++).
Palavras-chave: Dermatite alérgica de contato; Dermatite de contato; Diagnóstico; Testes cutâneos; Testes do emplastro

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[1] PhD. Assistant Professor at the Faculdade de Ciências Médicas da Santa Casa SP e Assistant at the Dermatology Clinic of the Santa Casa de São Paulo (FCMSCSP) – São Paulo (SP), Brazil.
[2] Specializing physician at the Dermatology Clinic of the Irmandade da Santa Casa de Misericórdia de São Paulo – São Paulo (SP), Brazil.
[3] Medicine graduation student at the Faculdade de Ciências Medicas of the Santa Casa de São Paulo (FCMSCSP) – São Paulo (SP), Brazil.
[4] Master – Assistant physician of the Dermatology Clinic of the Irmandade da Santa Casa de Misericórdia de São Paulo – São Paulo (SP), Brazil.

INTRODUCTION

Allergic contact dermatitis (ACD) is one of the most common skin lesions encountered in the daily practice of dermatologists. It is caused by substances capable of triggering a type IV immune reaction when in contact with an individual´s skin. [1,2,3]

ACD is most common in adults, especially in those whose professional activities are associated with exposure to various substances. [4-7] Among some populations studied, socio-economic differences and environmental factors influenced the prevalence of contact dermatitis. [6,8,9]

The contact test (patch test) is the most efficient method to confirm the etiological diagnosis of allergic contact dermatitis. A positive test, in the context of a relevant clinical history, can identify the materials that trigger the dermatosis. [6,10,11]

Recommendations include the use of a standard battery of substances for contact tests on ACD research. There are several standard test sets used in many communities, as suggested by the European group (International Contact Dermatitis Research Group - ICDRG), the American group (North American Contact Dermatitis Research Group - NACDRG) and the Brazilian group (Brazilian Contact Dermatitis Study Group - GBEDC). [12.13]

The interpretation of patch tests results follows a pattern set by the ICDRG, and includes either a negative reading or a positive reading with three degrees of intensity (+, ++ or +++). For most studies, the presence of a positive contact test (regardless of its intensity), associated with a relevant clinical history, confirms the diagnosis of ACD. [11, 12,13]

It is known that ACD appears each time a patient comes in contact with the etiologic agent, due to the presence of T lymphocytes, which act as memory cells and are produced at each new contact with the antigen. [9]

There are no studies in literature that compare the validity of positive contact tests results according to their intensity (+, ++ or +++).

OBJECTIVES

The objectives of this study were:

1) To determine the permanence of results between two patch tests performed with an interval of at least one year, in patients with a diagnosis of allergic contact dermatitis.

2) To determine the persistence of positive contact tests results according to their intensity (+, ++ or +++).

3) To evaluate the permanence of skin sensitization according to each substance tested.

METHOD

We conducted a clinical prospective (longitudinal) observational cohort study, using a consecutive non-probability sample, based on hospital.

Patients with a previous diagnosis of allergic contact dermatitis were selected. The diagnosis had been determined by positive contact tests carried out between the years 2005 and 2008, associated with a relevant clinical history. These patients were requested to attend the Clinic of Dermatology for new contact testing.

Patients included in the survey were submitted to a questionnaire about their behaviors for avoiding contact with ACD agents since the last testing, and, after signing an informed consent, each was subjected to a second series of tests using the same methodology as before. The minimum application interval between tests was 12 months and ranged from 12 to 60 months.

Both tests used the range recommended by the GBEDC in 1996, were approved by the National Sanitary Vigilance Agency (ANVISA) and manufactured by FDA Allergenic from Brazil (Rio de Janeiro), and were composed of 30 elements (Table 1). [12]

The tests were applied to the backs of patients using Finn Chambers retainers *(Epitest Ltd, Oy, Finland)*. After 48 hours, the tests were removed and the first reading was performed. The second reading was made after 96 hours. To measure the results, the 96-hour reading was used.

The criteria for reading the tests were the same ones adopted by the *International Contact Dermatitis Research Group* (ICDRG) in 1981. The following possible results were considered: (-) negative, (+) positive with some slight erythema and papules; (++) positive with erythema, papules and vesicles; (+++) positive with intense erythema, papules and confluent vesicles.

Among the tests, the presence or absence of negative and positive results, as well as the intensity of positivity, were evaluated. In addition, both tests were also compared for each substance tested.

The obtained data were entered into Microsoft Office Excel 2007 spreadsheet and analyzed. We used the SPSS software *(Statistical Package for the Social Sciences),* version 13, for nonparametric statistical calculations of the McNemar and Cohen's *Kappa* tests.

RESULTS

Among the 261 patients diagnosed with ACD who were requested to participate in the study, only 53 (20%) attended the clinic. Of those, only two had relative contraindications to the testing: pregnancy and use of immunosuppressive drugs. Two other patients were also excluded: one for showing excited skin syndrome, and the other for non-attendance to

Table 1: Battery of contact tests

Substance	Conc. (%)	Vehicles.	Substance	Conc. (%)	Vehicles.
Anthraquinone	2.0	vas.sol	Neomycin	20.0	vas.sol
Balsam of Peru	25.0	vas.sol	Nitrofurazone	1.0	vas.sol
Benzocaine	5.0	vas.sol	Parabens (2)	12.0	vas.sol
Potassiumbichromate	0.5	vas.sol	Paraphenylenediamine	1.0	vas.sol
P-TertiaryButylPhenol	3.0	vas.sol	Perfume-mix (3)	8.0	vas.sol
Carba-mix (1)	3.0	vas.sol	PPD-mix (4)	0.6	vas.sol
Cobaltchloride	1.0	vas.sol	Promethazine	1.0	vas.sol
Colophony	20.0	vas.sol	Propyleneglycol	1.0	vas.sol
Ethylenediamine	1.0	vas.sol	Quaternium 15	2.0	vas.sol
Formaldehyde	2.0	Water	Quinoline-mix (5)	5.0	vas.sol
Hydroquinone	1.0	vas.sol	Epoxyresin	1.0	vas.sol
Irgasan	1.0	vas.sol	Nickelsulphate	5.0	vas.sol
Kathon CG	0.5	vas.sol	Turpentine	10.0	vas.sol
Lanolin	20.0	vas.sol	Thimerosol	0.1	vas.sol
Mercaptobenzothiazole	1.0	vas.sol	Thiuram-mix (6)	1.0	vas.sol

(1) diphenylguanidine
(2) butyl, ethyl, propyl, methyl paraben, 3% each
(3) Eugenol, isoeugenol, cinamic alcohol, cinamicaldehide, geraniol, hidroxicitronellal, alpha-amyl cinamic alcohol, oakmoss absolute, 1% each.
(4) N-phenyl-n-cyclo-hexyl-p-phenylenediamine, N-iso-N-phenyl-p-phenylenediamine, N-diphenyl-p-phenylenediamine, 0.2% each.
(5) Clioquinol, clorquinaldol, 3% each.
(6) tetramethylthiuramdisulphidetetramethylthiurammonossulfite, tetraetiltiuramdisulphidedipentametilenetiurammonossulfite, 0.25% each.
Source: GBEDC, 2000.12

the results reading. Thus, the study was conducted with a sample of 49 individuals.

The study sample was comprised of 29 females and 20 males. There were 25 Caucasian and 24 non-Caucasian participants. The mean age was 44.9 years (range: 9-75, SD: 16.14).

In relation to the questionnaire responses, 18 subjects (37%) denied avoiding contact with allergenic substances at the previous test. On the other hand, 31 patients (63%) took measures to prevent the recurrence of symptoms. However, all patients found it difficult to completely eliminate the sensitizing agent. Among the 31 patients who tried to avoid contact, five of them (10%) reported a change in occupation, five (10%) reported use of protective equipment such as gloves and boots and 21 (43%) reported withdrawal/substitution of products with respect to allergenic substances (Table 2).

The results of both contact tests, containing each of them 30 substances analyzed, were compared for the 49 patients; thus, there were a total of 1,470 results from the first test to be compared with the retesting.

Regarding the first contact tests performed, of the 1,470 results, 1,321 (90%) were negative (last column of table 3) and of those, 1,263 remained negative in the second test (96%) and 58 (4%) became positive (+) without a consistent clinical history. No initial negative test became positive with an intensity of (++) or (+++) (first row of table 4).

In addition, during the first test, 77 (5.2%) results had a positive intensity (+), with 50 becoming negative at the second test; 26 remained (+) and one test had a (++) intensity. So it was observed that 65% of positive tests (+) became negative (second row of table 4).

The positive tests (++) in the first test occurred in 62 results (4.2% of all samples). At the retest, 42 remained (++), four became (+++), seven became (+) and nine became negative. Thus, 86% of tests (++) remained positive (third row of table 4).

Regarding the (+++) tests, there were 10 in the first test, all of which remained positive in the retest at the same intensity level (fourth row of table 4).

Table 2: Conduct of patients after the first contact testing

Conduct	Number	%
Change of occupation	5	10
Use of protective equipment	5	10
Replacement/abandonment of products with the allergen	21	43
Did not change habits	18	37
Total	49	100

Table 3: Interpretation of Kappa Index

Values of Kappa	Interpretation
<0	No agreement
0-0.19	Poor agreement
0.20-0.39	Fair agreement
0.40-0.59	Moderate agreement
0.60-0.79	Substantial agreement
0.80-1.00	Almost perfect agreement

Source: Landis JR, 1977. [14]

Calculation of the Kappa agreement index between the two tests, from the results listed in table 4, demonstrated a value of 0.531. However, by ignoring all the (+) positive results, the recalculated Kappa index was 0.888. These results were significant at 3.5% and 3.0%, respectively (both less than 5%), calculated by the software program SPSS.

The interpretation of Kappa values was based on literature data suggested by Landis JR e Koch GG (Table 3).[14] Therefore, the index reflected a moderate agreement between the tests, when taken into account all possible results, and excellent when it disregarded the positive (+).

Another approach to data interpretation was a specific analysis of the results for each substance tested. Some tests, such as anthraquinone and p-tertbutylphenol, were all negative, precluding any interpretation of the results.

Most substances showed only negative and positive results (+), with few positive results of intensity (++) and (+++), and even fewer that were maintained across the two tests.

A few substances showed positive results of intensity (++) and (+++) that were consistent between the tests, such as nickel sulfate and potassium bichromate (with a Kappa agreement index of 0.74 and 0.77, respectively). Using the McNemar test, we observed that there was no statistical significance for change between these tests, that is, the pattern remained.

DISCUSSION

The most significant challenge in this study was the loss of enrolled patients, since most of them did not attend the clinic (80%).

Regarding the epidemiological profile of the population assessed, there was compatibility of the results of this study with data from the literature: a predominance of females, Caucasian ethnicity and adult age range. [4-9]

It was observed that a percentage of patients (37%) showed resistance to changes in lifestyle that would be required for the effective treatment of allergic contact dermatitis; thus, symptoms persisted. Even among those who reported avoiding contact with allergens, many admitted not rigidly following guidelines because many sensitizers were present in the daily routine of the patients. The maintenance of exposure to sensitizing agents probably contributed to the positive tests and even to the exacerbated intensity of the positivity of some tests.

According to analysis of comparative results between both contact tests performed, patch tests showed to be reliable for negative and positive tests of (++) or (+++) intensity, because they remained the same with an agreement index classified as excellent. On the other hand, the positive tests of intensity (+) represented a possible transient sensitization, that should not be valued, because they did not remain consistent between the two testing periods and demonstrated no relevance with a patient's clinical history.

Some positive tests (++) became negative. This may be explained by the absence of contact by patients to the sensitizer, thus leading to negative tests resulting from the loss of sensitization.

The majority of substances tested showed only negative or mildly positive results (+), and were generally not consistent between the two tests, which may represent a less intense transient sensitization. Those with a number of positive results of (++) and (+++), such as nickel sulfate and potassium bichromate, result in a clinically relevant lasting sensitization.

Table 4: Overall results of the first and second performed contact tests

		2nd test				
		Negative	Positive +	Positive ++	Positive +++	Total
1st test	Negative	1263 (85.9%)	58 (4%)	0 0	1321 (90%)	
	Positive +	50 (3.4%)	26 (1.8%)	1 (0.1%)	0 77 (5.2%)	
	Positive ++	9 (0.6%)	7 (0.5%)	42 (3%)	4 (0.3%)	62 (4.2%)
	Positive +++	0 0	0 10 (0.7%)	10 (0.7%)		
Total		1321 (89.9%)	91 (6.2%)	43 (2.9%)	14 (1%)	1470

CONCLUSION

Contact tests proved to be reliable for negative and positive (++) and (+++) results, reflecting the permanence of results related to the sensitization of each individual. However, for the positive (+) results, the tests were not reliable and should not, in these cases, be relied on for clinical practice.

Moreover, some substances, such as nickel and potassium bichromate, were related to a lasting and intense sensitization and their results should be valued in practice; other substances results demonstrated a sensitization that was generally weak, transient and not clinically relevant.

Although the results of these contact tests confirm the etiology of ACD, patients find it difficult to eliminate the sensitizing agent, both due to the presence of the antigen in various substances that are part of their daily routine, and to the inability to follow appropriate guidelines. ❑

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Endereço para correspondência / Mailing address:
Ida Alzira Gomes Duarte
Rua Dr. Cesário Mota Jr, 61 - Santa Cecília
01221-020 - São Paulo, SP
Phone: +55 (11) 2230501
E-mail: idaduarte@terra.com.br

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