Course notes

Value and impact of patch testing in patients with allergic contact dermatitis

Valoarea şi impactul tehnicii *patch*-testării la pacienții cu dermatită de contact alergică

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Abstract

Contact dermatitis (eczema), entity recognized since ancient times, requires certain inflammatory reactions in the skin from direct contact with harmful environmental agents, representing 4-7% of dermatologist patients. There are two forms of contact dermatitis, irritant and allergic, at an incidence ratio of 4:1. Patch testing is the predominant method of establishing cause of contact allergy. Patch testing technique has undergone a continuous development and improvement since its first application in the 19th century; the bioassay proved to be a very effective tool for determining the status of a patient allergic sensitization, especially if performed in optimal conditions and competently interpreted. Recent efforts converge towards ideal patch test, free of side effects and no evidence of false-positive or false-negative reactions.

Keywords: *allergic contact dermatitis, sensitization, allergen, patch test.*

Rezumat

Dermatita (eczema) de contact, entitate recunoscută din vremuri antice, presupune existența unei reacții de tip inflamator din partea tegumentului, la contactul direct cu agenți nocivi din mediu, reprezentând 4-7% din cazuistica medicului dermatolog. Dermatita de contact cunoaşte două forme, iritativă şi alergică, aflate într-un raport de incidență de 4:1. Patch testarea reprezintă metoda prin care poate fi identificată cauza alergiei de contact. Tehnica patch testării a cunoscut o perpetuă dezvoltare şi îmbunătățire de la prima sa aplicație în secolul 19, acest biotest dovedindu-se un instrument foarte eficient pentru determinarea stării de sensibilizare alergică a unui pacient, mai ales dacă este efectuat în condiții optime şi interpretat în mod competent. Eforturile recente converg spre realizarea patch-testului ideal, lipsit de reacții adverse şi fără prezența de reacții fals-pozitive sau fals-negative.

Cuvinte cheie: *dermatita de contact alergica, sensibilizare, alergen, patch test.*

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General consideration

Allergic contact dermatitis is due to an antigen-specific cellular immune response that requires prior recognition of the trigger agent. This disease is therefore due to the contact between a certain substance and the individual skin which has suffered a specific reactivity variation. Allergic contact dermatitis is based on the pathophysiological mechanism of delayed hypersensitivity (type IV reaction), eczema caused by sap of poison ivy contact being a typical example (2). The skin is an effective protective barrier, but is subject to multiple and varied action of potential allergens involved in a perpetual dynamic in the context of modern advanced technology. Often, the trigger toxic agent is part of the composition materials that are handled in daily work. In this case we talk about professional or occupational contact dermatitis. World Health Organization statistics register every year over 2 million new cases of professional dermatitis, 35% of this are contact dermatitis. It is considered that over a quarter of the substances used in various processes in industry are harmful to human skin, and half of the diseases produced are allergic.

Considered the "father of patch testing", Josef Jadassohn (1863-1936) launched in 1895 this new technique after observing the onset of contact dermatitis from mercury. Later, his disciple Marion Sulzberger was the initiator of the bioassay in the United States and Alexander Fischer is known today as the one who propagated and improved the technique on the American continent being considered the greatest expert in contact dermatitis (3).

Today efforts are submitted to determine more precisely the relevance of positive patch test results, it is considered an important goal in dermato-allergology (4).

The purpose of Patch Testing

Diagnosis of allergic contact dermatitis involves two stages: the establishment of delayed hypersensitivity and patient exposed demonstration to some sensitization, both processes of this type of condition warranting investigation. Delayed hypersensitivity can be demonstrated in vivo by applying patch testing and in vitro by performing lymphoblastic transformation tests.

Patch testing is the best method for diagnosis the contact allergy (delayed hypersensitivity), this technique being superior over in vitro tests because the advantage of skin testing, the target organ for allergic contact dermatitis. Patients with relevant history of contact dermatitis is re-exposed to a suspected allergen to be the causative, exposure takes place under safety controlled conditions to verify the diagnostic.

Patch test application guidelines are:

- Cases of allergic contact dermatitis;
- Suspected contact allergy to topical applied drugs and some of their ingredients;
- Other types of eczema (hand eczema, atopic dermatitis, seborrhea, stasis) and dermatoses (psoriasis, lichen planus) where is suspected a contact allergy, especially given a high degree of recurrence and in the context of previous non-responsive treatment;
- Test the prediction for recommending alternatives to certain cosmetic products, perfumes, drugs, etc.

Clinical trials demonstrate the beneficial effect of this method on patients and their positively influence on the quality of life (5,6). However, random testing of patients, even with baseline series of tests is not recommended (7) due to the fact that patch test is considered a biological provocation test. In this sense, when we want to perform this bioassay have to pay attention to certain factors relating to test material, test system, functional and biological status of the person tested and not least the competence and experience of the doctors who performed (8).

Patch Testing principles

Patch-test is a useful way for investigating the allergic contact dermatitis demonstrating objectively that a particular allergen is able to induce

lesions for which patient consults a dermatologist, reproducing them artificially. Carried out appropriately by experienced doctors, this test enjoys a high sensitivity and specificity (9). In the last decades have been worked to standardize allergens, their vehicle, concentrations, patch testing materials and their score to get a safe method of great accuracy and good reproducibility. This standardization facilitated comparative studies between different geographical areas, types of contact allergies, with varying degrees of industrial areas (10,11). There have been described over 4000 substances responsible for producing allergic contact dermatitis (12) and new data are being published.

Application technique is relatively simple and consists in applying the test substance (usually allergen reactogenicity) in small amounts of dilution on the intact skin surface of the patient, under bandage occlusion for a determinate period of time (48 hours). To obtain an optimal bioavailability, must take into account the following factors: the molecule's strong allergen applied penetration ability, its concentration and dose, the vehicle in which is transported, the occlusion patch and exposure.

In practice we can distinguish two systems of patch testing: the original system in which allergens, patches and tapes are supplied separately and the ready-to-use system in which materials are prepared before and only applied. The first system, the original implies the existence of round aluminum enclosure with a diameter of 8 or 12 mm (Finn chambers) or square enclosure (van der Bend or IQ Chambers). Allergens should be as chemically pure (13), they are contained in plastic syringes or inert material bottles and must be stored under appropriate conditions of temperature, humidity, light, being renewed in accordance with the validity dates. Each allergen is in a vehicle, white petrolatum is the most common and preferred because offer a good occlusion, allergen stability and reasonable cost. Finn Chambers recommend the use of 20 mg of white petrolatum for obtaining an optimal dose of allergen (14). There are vehicles also used as liquid water and some solvents (acetone, ethanol), but the most modern are considered hydrophilic gels (cellulose derivatives). In the original system, the applied bands were made of colophony (cause severe and lasting reactions), but were replaced by modern acrylate-based adhesive tapes.

In ready-to-use system (TRUE test system) (15), the 28 allergens are incorporated in hydrophilic gels and patches are 9 to 9 mm is usable, but more expensive than that described above.

Preferred areas for allergens application are the supero-posterior chest (par vertebral and interscapulo-humeral), applying bands by exerting a light pressure, from the bottom up. If the patient has active lesions on the mentioned areas may be considered other areas such as front of forearm, the internal and external arms or external region of the thighs. The test is maintained 48 hours after that the reading is done, usually 20 minutes of lifting, then at 24, 48 and even 72 hours. Patients undergoing this allergy testing should be informed to avoid activities or sports that result in sweating, irradiation and grooming areas involved. The doctor should also explain local contraindications related testing periods to avoid aggravation of the disease, if generalized rash cortisone topics application and general contraindications such as systemic cortisone treatments, NSAIDs and immunosuppressant drugs. Regarding the per os treatment with antihistamines patch test application, is now considered as having no influence (16).

Today it is recommended to use standardized test antigens with optimal concentrations determined by international committees, antigens contained in the standard battery, as the European standard battery contains substances most commonly incriminated to cause contact dermatitis. Apart from standard kits are used specific antigen batteries adapted to various professions: dentists, nurses, housekeepers, hairdressers, masons, mechanics, etc. (17).

Physiological state of skin, allergen concentration and vehicle used, size of chambers, site and time of application, number of readings, all can influence the outcome and make possible multiple errors (18).

Reading, evaluation and interpretation of patch test reactions

Patch test reading results is based on morphological criteria, but the results interpretation should be done in a comprehensive way that includes the patient's medical history, clinical observations and exposure assessment.

In practice, should follow the differentiating the negative by positive reactions and the positive must be positioned on a quantitative scale. Note this: 0 / - negative reaction; ? doubtful reaction; 1 + weak positive reaction: erythema, infiltration, possibly papules; 2 + positive reaction: erythema, infiltration, papules, vesicles in almost 50% of the Finn chamber; 3 + intense positive reaction: erythema, infiltration, vesicles and bullous in more than 50% of the Finn chamber eventually coalescing; RI irritant reaction of different types; NT not tested.

Irritation may be caused by many allergens, differentiation between irritative and allergic response is often difficult to determine. Thus, allergic reactions are characterized by intense itching, extend beyond the Finn chamber and persist more time, while the irritation causes burning rather than reaction, does not extend over the edges of the test chamber and resolve sooner (19). Clinical skilled physician can analyze whether a demonstrated allergy may be responsible for determining contact dermatitis as a trigger or aggravating factor. This relevance to dermatitis trigger may be possible, probable or certain. The patch tests positivity absence does not prove the absence of allergy.

False positive patch test reactions

False positive reaction is a positive patch test reaction acquired in the absence of contact allergy (20).

A positive test interpretation need precautions, the false positive reactions are actually irritative erythema type reactions that can occur in certain situations such as:

- use of impure or contaminated antigens
- use of vehicle irritating substances (especially solvents) or irritating adhesive bands
- use of irritating antigenic mixtures (fragrance mix)
- use of high concentrations of antigen, with irritative effect, concentrations too high for the individual tested or ignores international standards settled
- application of substances with irritating and sensitizing double action (cement)
- cross-sensitivity, the presence of group effect (substances in "para" category: paraphenylenediamine, novocaine, sulfonamides, paraaminobenzoic acid, etc.)
- presence of acute or recent dermatitis at test
- multiple sensitizations due to tests contamination with low concentrations of related substances (metals allergy: over 30% of allergic patients are sensitized to nickel and chromium and 8% of those with chrome allergy have positive tests for nickel (16).

Sometimes the paraallergy phenomenon may occur. Thus, the simultaneous testing of several substances, some of which give strong positive reactions (3 +) can happen to have positive reactions with reduced intensity and other substances in the kit, substances normally used in isolation can cause negative reactions. Paraallergy phenomenon can be avoided by repeating the test separately for each substance that triggered the initial positive reaction.

Patients with a recent rash may develop hyperirritable skin which can cause to patch testing. Mitchell first called "angry back syndrome" (or excited-skin syndrome) to describe a regional phenomenon caused by the presence of strong positive reactions, skin hyperreactivity to a state of extensive interaction produced by several substances used for successive tests. With a frequency of about 40% cases of patients with repeated testing, the phenomenon means the erythematous plaques appearance on products reaction of successive test ingredients ("compound effect"), antigens commonly incriminated as epoxy resins, PPDA, neomycin,

primina, methacrylate and alanlactoses. It is therefore necessary to avoid patch testing in patients with skin instability with the presence of current dermatitis (21).

Another particular situation, common among repeated testing for nickel and thiuram is the “baboon syndrome" which involves inducing in some people with allergic ground plate erythematous vesicular often located on the thin skin subject to friction and hypersudoration (perigenital area, large folds, the buttocks area, front of thighs).

False negative patch test

False negative reaction is the negative patch-test reaction in the presence of contact allergy (20). As a positive reaction is not always a cause of contact dermatitis, so a negative result cannot exclude. Standard batteries in use include only statistically identified allergens as the most frequently responsible for producing contact dermatitis being absolutely necessary to keep a constant alerts in finding new and rare allergens.

The most common causes of false negative reactions are:

- quality of allergens: low concentration of the test substance (22), insufficient dose, inadequate vehicle (e.g. nickel in petrolatum)
- wrong technique of tests: inadequate application area, insufficient occlusion, duration of exposure too small, early reading or incomplete results
- absence (when testing) of predisposing factors normally present in the workplace: moisture, friction, pressure, irritants, etc.
- tests application, in some cases too far from lesions (existence of the skin "regional memory" to certain allergens)
- systemic administration of corticosteroids (false negative reactions are seen in patients with receiving systemic corticosteroids administered over 20 mg / day) or immunomodulators
- test site treatment with corticosteroids, ultraviolet or Grenz rays
- reduced cellular immunity of the elderly (the tests are read at 48-72 hours - "late positivity")
- sensitized patients over 3 years ago (25% have false negative reactions)
- compound allergy (patients with positive reactions to products made, but have negative reactions to their ingredients tested separately).

The safety profile of patch test technique

Is already known high safety profile of this test for patients with contact dermatitis. However, there were described some possible side effects or complications of patch-testing:

- active awareness
- non-standardized allergen irritative reactions, often on procured patient
- rash of pre-existing dermatitis due to percutaneous absorption of the allergen
- pigmentation disorders (e.g. phenols depigmentation or hyperpigmentation in place of testing after exposure to sunlight)
- hypertrophic or keloid scars
- granulomas (zirconium, beryllium), necrosis, Köbner phenomenon
- anaphylactoid or shock reactions (neomycin, bacitracin)
- viral or bacterial infections
- subjective phenomena related to patient

Conclusions

Patch testing remains the main lab method to confirm, in vivo, the delayed hypersensitivity, contact allergy. The permanent technical suffer improvements trying to approach an ideal standard in the lack of false positive or negative reactions, the absence of adverse reactions. Patch testing should be made competent by experienced physicians in the field who suspected a contact allergy and only after a case history and a detailed history combined with a thorough clinical examination.

Today, everyone recommends the use of standard battery of allergens with optimal bioavailability, with a consensus evaluation and

interpretation tests, batteries continuously adapted to changes that occur in exposure, the emergence of new allergens, recent international experience.

References

1. Coenraads P-J, Diepgen T, Uter W et al. Epidemiology.In: Frosch PJ, Menne T, Lepoittevin J-P, eds. Contact Dermatitis, 4th edn. Berlin: Springer, 2006: 135-63
2. Lachapelle JCh. Journees Nat Med Trav 1992 – Nantes – 311
3. Rietschel RL, Fowler JF Jr. Fischer´s contact dermatitis, 6th edn. BC Decker, 2008: Hamilton, Ontario
4. Lachapelle JM, Maibach HI. Clinical relevance of patch test reactions, Chapter 8. In: Lachapelle JM, Maibach HI (eds) Patch testing and prick testing. A practical guide. Springer, Berlin. 2009; 133-120
5. Thomson KF, Wilkinson SM, Sommer S, Pollock B. Eczema: quality of life by body site and the effect of patch testing. Br. J Dermatol 2002; 146:627-630
6. Woo PN, Hay IC, Ormerod AS. An audit of the value of patch testing and its effect on quality of life. Contact Dermatitis. 2003; 48:244-247
7. Van der Valk PGM, Devos SA, Coenraads P-J. Evidence-based diagnosis in patch testing. Contact Dermatitis. 2003; 48:121-125
8. Mowad CM. Patch testing: pitfalls and performance. Curr Opin Allergy Clin Immunol. 2006; 6:340-344
9. Nethercott JR, Cooley JE. Getting the most out of patch testing. Curr Opin Dermatol. 1995
10. Ale SI, Maibach HI. Reproductibility of patch test results: a concurrent right-versus-left study using TRUE test. Contact Dermatitis. 2004; 50:304-312
11. Schiessl C, Wolber C, Strohal R. Reproductibility of patch tests: comparison of identical test allergens from different commercial sources. Contact Dermatitis. 2004; 50:27-30
12. De Groot AC. Patch testing. Test concentration and vehicles for 4320 chemicals, 3rd edn. Wapserveen. The Netherlands. 2008
13. Ryberg K, Gruvberger B, Zimerson E, Isaksson M, Persson L, Sorensen O et al. Chemical investigations of disperse dyes in patch test preparations. Contact Dermatitis 2008; 58:199-209
14. Bruze M, Isaksson M, Gruvberger B, Frick-Engfeldt M. Recommandation of appropiate amounts of petrolatum preparation to be applied at patch testing. Contact Dermatitis. 2007; 56:281-285
15. Fischer T, Maibach HI. Easier patch testing with TRUE test. J Am Acad Dermatol. 1989; 20:447-453
16. Bucur G, Bucur L, Sălăvăstru CM, Țiplica G-S. Dermatoze profesionale. Ed.Niculescu 2006; 158
17. Bruze M, Salazar LC, Goossens A, Lanerva L, White I. Thoughts on sensitizers in a standard patch test series. Contact Dermatitis Volume 41, Issue 5, Nov. 1999; 241–250
18. Wahlberg JE, Elsner P, Kanerva L, Maibach HI. Management of positive patch test reactions. Springer, Berlin. 2003
19. Middleton E, Reed CE, Ellis EF et al. Allergy principles & practice. 1993, ed. IV, 1067
20. Rycroft RJG. False reactions to nonstandard patch tests. Semin Dermatol. 1986; 5:225-230
21. Cockayne SE, Gawkrodger DJ. Angry back syndrome is often due to marginal irritans: a study of 17 cases seen over 4 years. Contact Dermatitis. 2000; 43:280-282
22. Kanerva L, Estlander T, Jolanski R, Alanko K. False negative patch test reactions due to a lower concentration of patch test substance than declared. Contact Dermatitis. 2000; 42:289-291