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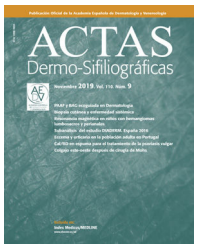

ORIGINAL ARTICLE

[Translated article] Contact Allergy in Patients With Rosacea

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Received 23 April 2021; accepted 27 February 2022
Available online 10 May 2022

KEYWORDS
Rosacea;
Contact dermatitis;
Patch tests

Abstract
Background and objective: Rosacea is a chronic acneiform skin disorder in which impaired skin barrier function can lead to sensitization to allergens. We aimed to analyze contact allergies in our patients with rosacea.
Material and methods: Retrospective cohort study of all patients who underwent patch testing in our skin allergy clinic between May 1991 and May 2019.
Results: A total of 200 patients with rosacea were referred to our clinic for patch testing during the study period; they represented 2.1% of all patch tested patients in the period. Eighty-one percent were women (mean age, 44.7 years). At least 1 positive patch test was recorded for 46.5%; 15% were of current relevance. The most frequent positive reaction was to nickel (26%), followed by cobalt chloride (6.5%), isothiazolinones (6%), p-phenylenediamine (5.5%), fragrance mix II (5%), and thimerosal (3.5%). The most common currently relevant patch test reactions were to isothiazolinones in 10 of the 200 patients (5%); to phenylenediamine, fragrance mix II, and toluensulfonamide formaldehyde resin in 4 patients (2%) each; and to tixocortol and fragrance mix I in 2 patients (1%) each. The allergen groups most often implicated were metals (of current relevance in 12.6%) and drugs (of current relevance in 25.8%). Preservatives and fragrances were the next most common allergen groups, and 70.8% and 43.7% of the positive reactions in these groups, respectively, were of current relevance. Cosmetics were the most frequent source of sensitization, followed by topical medications—notably corticosteroids and antifungal agents.

DOI of original article: https://doi.org/10.1016/j.ad.2022.02.026
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https://doi.org/10.1016/j.ad.2022.05.008

Conclusions: We emphasize the high prevalence of allergic contact dermatitis in patients with rosacea, a finding which supports patch testing, especially if eruptions worsen when these patients use cosmetics and topical medications.

PALABRAS CLAVE
Rosácea;
Dermatitis de contacto;
Epicutáneas

Sensibilización alérgica de contacto en pacientes con rosácea

Resumen

Introducción y objetivo: La rosácea es una dermatosis acneiforme crónica donde la disrupción de la barrera cutánea puede provocar una facilidad para la sensibilización a distintos alérgenos. Nuestro objetivo es analizar la sensibilización alérgica de contacto en los pacientes con rosácea de nuestro medio.

Material y métodos: Se realizó estudio de cohortes retrospectivo analizando todos los pacientes parchados en la consulta de Alergia Cutánea de nuestro servicio entre mayo de 1991 hasta mayo de 2019.

Resultados: Durante el tiempo de estudio han sido remitidos a nuestra consulta un total de 200 pacientes con rosácea, 2,1% del total de los pacientes parchados en este tiempo; 81% de los pacientes eran mujeres, con una edad media de 44,7 años; 46,5% presentaron al menos un parche positivo, considerándose de relevancia presente (RP) en 15%. Los parches positivos más frecuentes fueron níquel (26%), seguido de cloruro de cobalto (6,5%), isotiazolinonas (6%), PPDA (5,5%), mezcla II de perfumes (5%) y thiomersal (3,5%). Los parches positivos de RP más frecuentes fueron isotiazolinonas en 10/200 pacientes (5%), PPDA, mezcla II de fragancias, toluensulfonamida formaldehído resina en 4/200 pacientes cada uno (2%), tixocortol y mezcla I de fragancias en 2/200 cada uno (1%). El grupo de sustancias más frecuentemente detectadas fueron los metales, con una RP en 12,6%, seguido de los fármacos con una RP en 25,8%. Los conservantes y las fragancias fueron los siguientes grupos de sustancias más frecuentemente positivas, con una RP en 70,8 y 43,7%, respectivamente. La fuente de sensibilización más frecuente fueron los cosméticos, seguidos de los fármacos tópicos, destacando los corticoides y los antifúngicos tópicos.

Conclusiones: Destacamos una elevada prevalencia de dermatitis alérgica de contacto en pacientes con rosácea, lo que sustenta la realización de pruebas epicutáneas, especialmente en aquellos con empeoramiento de sus lesiones en relación con la aplicación de productos cosméticos o fármacos tópicos.

Introduction

Rosacea is a chronic inflammatory acneiform skin disorder that frequently affects the center of the face. It is characterized by episodes of transient flushing, persistent erythema, telangiectasias, papules, and pustules. Its estimated prevalence in our setting is 10%, and it commonly affects middle-aged women. Patients typically complain of ''irritable or sensitive skin'', which is defined as increased susceptibility or intolerance to exogenous products.[1]

The pathophysiology of rosacea is not well known. The various mechanisms reported to be involved in the onset of this condition include neurovascular dysregulation, abnormal innate immune response, or overgrowth of the mite *Demodex folliculorum*. Secondary disruption of the skin barrier has also been associated with rosacea.[2] This can cause irritation and facilitate sensitization to various allergens.[3] However, contact allergy in patients with rosacea has received little attention in the literature. A retrospective analysis of patients with rosacea and suspected contact allergy revealed that affected patients are at greater risk of contact allergy to propolis, the synthetic fragrance lyral, their own products, and metronidazole.[4]

The objective of this study was to analyze allergic contact sensitization in patients diagnosed with rosacea in our setting.

Material and methods

We performed a retrospective cohort study of all patients who underwent patch testing at the Allergy Clinic of Hospital General Universitario de Valencia, Valencia, Spain between May 1991 and May 2019. We selected patients referred to the clinic with a diagnosis of rosacea. We used the patch test database, which includes all patients who underwent patch testing between January 1980 and June 2019. In the cases selected, the patients had undergone testing with the standard series of the Spanish Contact Dermatitis and Skin Allergy Research Group (Grupo Español de Investigación en Dermatitis de Contacto y Alergia Cutánea [GEIDAC]), supplied by Marti Tor, and with additional series based on clinical suspicion in each case. The allergens were applied

to the patient's back on an area of seemingly healthy skin and occluded for 48 hours with Finn chambers supplied by Allergeaze. Readings were taken at 48 and 96 hours. The skin reaction was evaluated based on the criteria of the International Contact Dermatitis Research Group. The variables analyzed were sex, age, history of atopy, allergens, relevance, and source of sensitization. Polysensitization was defined as the presence of a positive result with at least 3 different allergens.

We performed a descriptive statistical analysis of all the variables, which were described using the mean (SD) for quantitative variables and percentages for qualitative variables. Hypotheses were assessed using the χ^2 test or *t* test depending on whether the variables analyzed were qualitative or quantitative, respectively. The statistical data were analyzed using SPSS for Windows, Version 21.0 (IBM Corp.). Statistical significance was set at $P < .05$.

Results

Between May 1991 and May 2019, a total of 200 patients were referred to the Skin Allergy Clinic of our department with a diagnosis of rosacea, that is, 2.1% of all patients who underwent patch testing during this period (9521). Males accounted for 19% (38/200) and females for 81% (162/200); mean age was 44.7 years. Over a quarter of the patients (29% [48/200]) had a personal and/or family history of atopy.

All the patients underwent patch testing with the standard GEIDAC series. Furthermore, the preservative series was used in 57/200 patients (28.5%), the cosmetic series in 15/200 (7.5%), and photopatch testing in 5/200 (2.5%).

Of all the patients studied, 93/200 (46.5%) had at least 1 positive result, which was of present relevance in 30/200 (15%). A total of 181 positive results were recorded, that is, a mean of 0.9 positive patch results per patient assessed. Polysensitization was detected in 22/200 (11%) patients. Positive results were not significantly associated with sex ($P = .6$), age ($P = .6$), or a history of atopy ($P = .76$).

The most common positive results were for nickel sulfate (52/200, 26%), followed by cobalt chloride (13/200, 6.5%), isothiazolinones (12/200, 6%), paraphenylenediamine (11/200, 5.5%), fragrance mix II (10/200, 5%), thiomersal 0.1% (7/200, 3.5%), caine mix (6/200, 3%), and potassium dichromate 0.5% (5/200, 2.5%).

The most common positive results with present relevance were for isothiazolinones (mix of methylchloroisothiazolinone/methylisothiazolinone and/or methylisothiazolinone alone) (10/200 patients [5%]), paraphenylenediamine, fragrance mix II and toluenesulfonamide formaldehyde resin (4/200 [2%] each), and tixocortol pivalate and fragrance mix I (2/200 [1%] each).

Table 1 shows the most common allergens by group of substances. We detected 79/181 positive results for metals, with present relevance in 10/79 (12.6%). The second most common group of substances was drugs, with 31/181 positive results and present relevance in 8/31 cases (25.8%). Preservatives and fragrances were next, with positive results in 24/181 and 16/181 and present relevance in 17/24 (70.8%) and 7/16 (43.7%), respectively.

The most common source of sensitization in patients with relevant positive results was cosmetics (76.6% of cases), mainly moisturizing creams, perfumes, hair dyes, and nail lacquer, followed by topical drugs (23.3%). The most commonly involved drugs were corticosteroids and topical antifungal agents.

Table 1 Most Frequent Positive Allergens by Group of Substances.

No. of positive results by group of substances	No. (%)
Metals	79 (43.6)
Nickel sulfate	52 (28.7)
Cobalt chloride	13 (7.1)
Potassium dichromate	5 (2.7)
Other (palladium chloride, gold sodium thiosulfate, mercury)	9 (4.9)
Drugs	31 (17.1)
Thiomersal	7 (3.8)
Caine mix	6 (3.3)
Neomycin, povidone iodine, hydrocortisone, ketoconazole, tixocortol pivalate, budesonide	2 (1.1)
Other (phenylephrine, ketoprofen, piketoprofen, fenofibrate)	6 (3.3)
Preservatives	24 (13.2)
Isothiazolinones	12 (6.6)
Toluene sulfonamide formaldehyde resin	4 (2.2)
Quaternium-15	3 (1.6)
Other (sodium metabisulfite, methyldibromo glutaronitrile, grotan BK)	5 (2.7)
Fragrances	16 (8.8)
Fragrance mix II	10 (5.5)
Fragrance mix I	4 (2.2)
Balsam of Peru	2 (1.1)
Dyes	13 (7.2)
Paraphenylenediamine	11 (6)
p-Toluenediamine sulfate	1 (0.5)
3-Aminophenol	1 (0.5)

Discussion

The pathophysiology of rosacea is unknown, although various etiological and pathogenic factors may be associated with its development, principally alteration of vascular reactivity, the immune response to microorganisms such as *Demodex folliculorum*, and an impaired skin barrier with an exaggerated response to external agents.[2] Furthermore, clinical expression of the disease, which worsens in the face of various environmental factors and is characterized by intolerance to topical products, leads patients themselves to consult a dermatologist to assess a possible ''skin allergy''. While rosacea has clearly been shown to predispose patients to ''sensitive skin'' and, therefore, leave them more likely to have irritant contact dermatitis, patch testing can help to optimize diagnosis and therapy in patients affected by this condition.

It is noteworthy that 46.5% of patients with rosacea who underwent patch testing in our study had at least

1 positive result. This percentage is similar to the 38.2% reported by Jappe et al.[4] among the 361 patients they analyzed. This prevalence is greater than that reported for other types of inflammatory skin disease, such as psoriasis,[5] possibly because of the association with the etiologic-pathogenic hypothesis of an impaired skin barrier that favors the development of allergic contact dermatitis in patients with rosacea. Medgyesi et al.[2] showed that papulopustular rosacea involves impairment of the stratum corneum and reduced intracellular lipids and antimicrobial peptides, as occurs in atopic dermatitis.

A detailed analysis of the results of patch tests in patients with rosacea from the main published series shows the most frequent allergen to be nickel sulfate, followed by balsam of Peru, propylene glycol, methyldibromo glutaronitrile, gentamicin sulfate, fragrance mix, and thiomersal, depending on the series.[3,4,6] Nickel sulfate was also the most frequently detected allergen in our series, with a frequency of sensitization of up to 26%, which, while consistent with the prevalence among the general public in our setting,[7] is higher than that reported for the population of Europe (14.5%).[8] However, although metals—including cobalt chloride and potassium dichromate—are among the most frequently reported allergens in studies analyzing the prevalence of sensitization in patients with rosacea, a critical analysis of the results indicates that most cases involve past relevance.[7] Moreover, while it has been postulated that trace amounts of metal in cosmetics (especially those applied on the eyes, such as pencils and shadow) could trigger allergic contact dermatitis,[9] most positive results for metals in patients with rosacea are of past or unknown relevance. Also noteworthy is the higher prevalence found for allergic contact sensitization to fragrance mix II than to fragrance mix I, in contrast with findings traditionally reported in the literature,[10] although in recent years, this trend seems to have leveled off, consistent with data in our study,[11] possibly owing to the increased presence of these substances in facial cosmetics.

Few articles analyze the relevance of the various patch tests in patients with rosacea. Relevance plays a key role in our interpretation of the results and in the practical implications of patch testing in the management of affected patients. In our study, the analysis of the relevance of positive results showed fragrances and preservatives to be the most common relevant allergens. This finding is consistent with those of Pónyai et al.,[12] who highlighted balsam of Peru and fragrance mix as the most relevant allergens. In this sense, many studies stress that allergens associated with cosmetics are more frequent in patch testing of patients with rosacea, as reported by Diczig et al.,[6] who found the most common allergens to be balsam of Peru (9/143 [6.3%]), propylene glycol (6/143 [4.2%]), lanolin (5/143 [3.5%]), and paraphenylenediamine (5/143 [3.5%]). In fact, examination of patients with rosacea should be complemented with the cosmetic series in order to extend the diagnostic capacity of the dermatologist.

Therefore, the most common relevant allergens in patients with rosacea are fragrances and preservatives, with the usual sources of sensitization being facial cosmetics, i.e., rinse-off cosmetics (gels, make-up remover) and leave-on cosmetics (mainly moisturizing cream). The main preservatives involved are the isothiazolinones, which have become a major cause of skin allergy in the general population during recent decades, to the extent that sensitization by these substances can now be considered epidemic. Fortunately, updates to European Union regulations have markedly reduced the incidence of sensitization.[13] Other common allergens that should be highlighted in patients with rosacea include the components of hair dyes (paraphenylenediamine) and the components of cosmetic products used for nail care (mainly toluenesulfonamide formaldehyde resin).

Given that allergens in cosmetics are the most common in patients with rosacea, examination should be complemented by application of additional commercial allergen series, especially the cosmetics series. Furthermore, we wish to highlight the usefulness of including the patient's own cosmetic products in the examination, both as a repeat open application test and a patch test. In addition to cosmetics, topical drugs may be associated with allergic contact dermatitis in patients with rosacea, especially antibiotics, antifungal agents, corticosteroids, and nonsteroidal anti-inflammatory drugs. Therefore, the possibility of iatrogenic allergic contact dermatitis should be taken into account in patients with rosacea, mainly in those whose lesions have worsened.

In conclusion, we highlight the high prevalence of allergic contact dermatitis in patients with rosacea, thus supporting the use of patch tests in this population, especially in those whose lesions worsen with the application of cosmetic products or topical drugs. Thus, the study of skin allergy could prove useful in patients with rosacea in terms of secondary prevention through allergen avoidance, although it can also play a role in primary prevention. Recommended measures should include use of fragrances that do not contain potentially sensitizing fragrances or preservatives[14] and avoidance of hair dyes and nail care cosmetics. Furthermore, informing patients with rosacea about the possibility of repeat open application testing or cosmetic use testing before regular application of products could help to optimize clinical management. It is also important to bear in mind that topical drugs used for treatment of rosacea may also worsen the condition and should therefore be considered potential allergens (both the active ingredients and the excipients) in the diagnostic work-up.

Conflict of interest

The authors declare that they have no conflicts of interest.

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