

ORIGINAL ARTICLE

Contact allergy in patients with rosacea: a clinic-based, prospective epidemiological study

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Keywords

antibiotics, contact dermatitis, cosmetic allergy, fragrances, medicaments, preservatives, rosacea

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Received: 12 November 2007,
accepted 18 March 2008

DOI: 10.1111/j.1468-3083.2008.02778.x

Abstract

Background Rosacea is a relatively common inflammatory skin disease of unknown prevalence. The proportion of contact allergy complicating rosacea and its therapy, respectively, is largely unknown.

Objective To estimate the prevalence of specific contact allergy in rosacea patients and to compare this with the prevalence observed in the general population and in general patch test patients.

Patients/methods In this prospective monocentre study, 78 patients with rosacea were investigated for contact sensitizations via patch testing the standard series, constituents of topical formulations, preservatives, fragrances, topically applied drugs and, if available, patient's own products.

Results Positive reactions occurred to nickel (II) sulphate (12 of 78, 15.4%), fragrance mix I (4 of 77, 5.2%), balsam of Peru (8 of 77, 10.4%; significantly elevated prevalence compared to that observed in the population-based KORA study), potassium dichromate (4 of 78, 5.1%) and Lyril (3 of 78, 3.8%). Regarding topical antibiotics, only 1 of 78 (1.3%) patients was positive to neomycin sulphate, and none to metronidazole; however, 6 of 75 (8%) patients were positive to gentamicin sulphate, and 4 of 76 (5.3%) patients were positive to framycetin sulphate. No allergic but irritant patch test reactions, instead, were provoked by various patients' own products as well as by the irritant sodium lauryl sulphate (SLS) even in low concentrations.

Conclusion Despite the limited power of the study, a strikingly high prevalence of contact allergy to gentamicin sulphate was observed, which is probably due to antibiotic treatment of rosacea-associated eye symptoms. The reactions to the irritant SLS probably mirror the extreme skin sensitivity in rosacea.

Introduction

Rosacea is a common disorder, especially in fair-skinned individuals, characterized by flushing, erythema, papulopustular eruptions and rhinophyma.¹ About 1% of all patients seen in dermatology departments suffer from rosacea.² Exact incidence or prevalence data on the population level are, however, lacking.³

The underlying pathomechanisms are still a matter of discussion.^{4,5} Genetic, environmental, vascular and microbial factors such as *Helicobacter pylori* and the proteases of *Demodex folliculorum* have been identified as possible triggers of rosacea.³ Acne vulgaris has been shown to precede rosacea, as have been contact dermatitis and long-standing glucocorticosteroid therapy (fig. 1). As there is no cure of this facial disease, therapy focuses on suppression

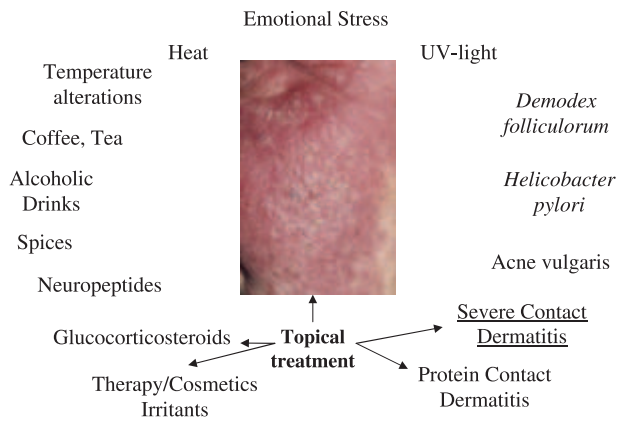


fig. 1 Triggers for rosacea

of inflammation, erythema and teleangiectasia. Whereas for the vascular component, a pharmacological approach has not been proven to be successful and laser treatment, although successful in the first place, does not prevent relapse, inflammation responds well to systemic and topical antibiotics. It is, however, definitely not the antimicrobial effect that induces resolution⁴ but may be due to their anti-inflammatory and immunosuppressive properties. Rosacea patients often observe unexplained aggravation of erythema, scaling and/or itching in the course of the disease. Another typical feature is the 'irritable skin of rosacea patients' characterized by burning and stinging⁶ and an increased susceptibility to adverse reactions caused by external formulations. This can make the choice of local treatment and skin-care products extremely difficult. Whereas the irritating potential of formulations (gel vehicles and creams) have been addressed in studies,^{7,8} there are still only few data on contact allergy in rosacea patients, the majority being case reports.^{9–11} This is astonishing, as sensitive and inflamed skin may be more prone to contact sensitization,^{12–15} and coexistence of both phenomena in rosacea patients is probably not uncommon. A retrospective analysis on patients with rosacea and additionally suspected contact allergy revealed that this group of patients had a higher risk of contact allergy to propolis, the synthetic fragrance Lyrall®, own products and, possibly, metronidazole.¹⁶ Encouraged by these results, this systematic prospective investigation of rosacea patients for contact sensitizations addressed the following questions:

- 1 How frequent is contact allergy to generally important allergens, and to topical medications used for treatment in patients with rosacea?
- 2 How does this frequency relate to that observed in the general population of similar age and sex distribution?

These research questions cannot validly be addressed by analysing data of patients patch tested for suspected allergic contact dermatitis. Instead, all rosacea patients attending the clinic were patch tested, irrespective of this standard indication.

Materials and methods

Study population

The study was approved by the Ethical Committee, University of Heidelberg. From January 2004 to November 2006, 78 patients, referred by dermatologists or general practitioners, or consulting by their own intention, fulfilled the case definition of the study (primary diagnosis of rosacea, made on the basis of history and clinical criteria according to Wilkin *et al.*¹ possibly in addition to other diagnoses, and written informed consent) and were hence included in the data analysis using the Information Network of Departments of Dermatology (IVDK; www.ivdk.org) infrastructure.¹⁷ Although this investigation was performed only at the University of Heidelberg, all data were as usually transmitted in an anonymous, electronic format to the data centre of the IVDK in Goettingen, quality controlled and subsequently analysed.

Patch test procedure

Patch tests were performed according to the international guidelines of the International Contact Dermatitis Research Group,¹⁸ further extended by the German Contact Dermatitis Research Group (DKG).¹⁹ Patch test substances were obtained from Hermal (Reinbek, FRG). Patch test exposure time was 2 days. Results presented are based on readings 72 h (day 3) after the start of application of patch test material, as recommended by the guidelines.

The following allergens were included using predefined patch test series of the DKG (www.ivdk.org/dkg/dkgblo.html): the standard series, constituents of topical formulations, preservatives, fragrances in addition to the fragrance mix I and II²⁰ included in the standard series, glucocorticosteroids (prednisolone, hydrocortisone-17-butyrate, clobetasol-17-propionate, triamcinolone-acetonid, dexamethasone-21-phosphate disodium salt, amcinonide, betamethasone-17-valerate, hydrocortisone, budesonide), topically applied antibiotics (i.e. chloramphenicol, neomycin sulphate, framycetin and gentamicin). Additionally, the following antibiotics, which are frequently used for topical treatment of rosacea (clindamycin 1%, erythromycin 4% and metronidazole 2%), all in petrolatum, were especially prepared and provided by the university hospital pharmacy. All test substances except formaldehyde, MCI/MI and chlorhexidine digluconate, which were diluted in water,

were dispersed or dissolved in petrolatum. In addition to standardized patch test series, patient's own products, if presented, were also patch tested, consisting of topical medications (among them 12 original metronidazole-containing ointments) and skin care products, rinse-off as well as leave-on products. Patch test reactions between '+' and '+++' at day 3 were considered positive.

Additionally, the irritant sodium lauryl sulphate (SLS) was patch tested in each patient using three different concentrations (0.25%, 0.5%, 1.0% in water), as there is evidence that a higher skin susceptibility as indicated by a reaction to SLS may induce non-specific erythematous or weak positive reactions to contact allergens in patch testing.

Data handling and statistics

Data analysis was done using the statistical program system SAS (version 9.1.3, SAS Institute, Cary, NC, USA). The proportions of patients with positive reactions were given both as crude prevalence values, and as prevalence standardized for age and sex, following the IVDK standards. The proportions were supplemented with 95% confidence intervals (95% CIs) to address precision, following current relevant guidelines.²¹

Results

Seventy-eight rosacea patients who were referred to the Department of Dermatology, University of Heidelberg, between 2004 and 2006 were included in a prospective investigation for contact sensitization using standard commercial test series. Twenty-one participants were additionally patch tested with their own cosmetics/medical treatments with a total of 133 single patch tests.

Although other than in routine patch testing the patients had not been specifically selected for suspected allergic contact dermatitis, in 19 (24%) allergic contact dermatitis patients were suspected (i.e. the typical indication for diagnostic patch testing was present). Among the 78 patients, 40 (51%) were male. The median age was 60 years, interquartile range was 50 to 69, range was 25 to 81. In accordance with the age distribution, many were old age pensioners ($n = 36$) or not employed ($n = 6$), some office workers ($n = 12$), house wives ($n = 4$) or working in various, mostly singular occupations. Past atopic dermatitis was recorded in 4 (5%) patients. Application of cosmetics and skin care products ($n = 65$) and topical medications ($n = 55$) was often suspected to negatively affect the skin; however, only in 17 cases had allergic contact sensitization been suspected in pre-patch test assessment. As a result of patch testing, 49 of 78 patients (23 of 40 [51.3%] male, 26 of 38 [48.7%] female) showed at least one positive reaction

to commercial test substances. Among the 49 patients mentioned, 34 had at least one positive reaction to allergens of the standard series (44% of all study participants). The most common allergens are listed in Table 1. Altogether, 5 of the 78 patients reacted to the fragrance mix I or its constituents. Only 1 of 76 patients was positive to neomycin sulphate, and none was sensitized to chloramphenicol, erythromycin, clindamycin and metronidazole. Interestingly, 6 of 75 (8%) patients tested positive to gentamicin sulphate, and 4 of 76 (5.3%) patients were positive to framycetin sulphate. None of the rosacea patients had a contact sensitization to topically applied glucocorticosteroids.

In an additional age- and gender-stratified analysis [4 strata: men (women) 60 or less vs. 61 or more], nickel sensitization in our study population was found to predominantly occur in younger female patients, which was to be expected and has no association with rosacea. Sensitization to balsam of Peru, however, showed a surprising increase in men aged 60 or younger.

Patients own products including topical medical treatment

The phenomenon of 'irritable skin of rosacea patients' characterized by burning and stinging and an increased susceptibility to adverse reactions caused by external formulations prompted additional patch testing of patients' own products to rule out contact allergy to these products. The products were categorized into one of 24 categories, based on an EU classification (annex I to 76/768/EEC²²). None of these products yielded positive, but only induced a couple of doubtful or irritant reactions, the product categories being deodorants and antiperspirants ($n = 2$; negative); anti-wrinkle products ($n = 1$; negative); products for making up and removing make up from the eyes ($n = 2$; negative); hairdressing products (lotions, lacquers, brilliantine; $n = 2$; 1 irritant reaction); hair cleaning products (lotions, shampoos, powders; $n = 4$; 1 irritant reaction); cosmetic cleaning products (excl. soaps and medicated products; $n = 2$; 1 irritant reaction); topical medical formulations ($n = 34$; negative); metronidazole preparations ($n = 12$; negative); 'medical' cosmetics (OTC; $n = 1$; negative); perfumes, toilet waters and eau de Cologne ($n = 3$; negative); creams, emulsions, lotions, gels and oils for the skin (hands, face, feet, etc.; $n = 33$; negative); shaving products (creams, foams, lotions; $n = 2$; negative); toilet soaps, deodorant soaps, etc. ($n = 2$; negative); products for making up and removing make up from the face (excl. eyelids; $n = 5$; negative); sunbathing products ($n = 6$; 1 irritant reaction).

None of the patch test-positive rosacea patients experienced a flare-up of the underlying disease. The analysis of

Table 1 Prospective analysis results of contact sensitization in rosacea patients for the most common allergens, preservatives and topical drugs, and fragrances (readings 3 days after start of patch test). Crude age- and sex-standardized proportions with respective 95% CI. Singular positive reactions not included

Substance	Concentration (%)	N (positive/tested)	% positive	Exact 95% CI	% positive standardized ²¹	95% CI
Nickel (II)-sulphate	5.00	12/78	15.4	(8.2–25.3)	39.7	(35.2–44.2)
Methyldibromo glutaronitrile	0.30	5/54	9.3	(3.1–20.3)	4.2	(0.5–7.8)
Potassium dichromate	0.50	4/78	5.1	(1.4–12.6)	12.8	(0.0–34.1)
Colophony	20.00	2/78	2.6	(0.3–9.0)	1.4	(0.0–3.5)
Gentamicin sulphate	20	6/75	8.0	(3.0–16.6)	14.3	(0.0–35.8)
Framycetin sulphate	10	4/76	5.3	(1.5–12.9)	3.4	(0.1–6.8)
Benzophenon-4 (Sulisobenzon)	10	2/77	2.6	(0.3–9.1)	1.0	(0.0–2.3)
Tert. butylhydroquinone	1.0	3/78	3.8	(0.8–10.8)	6.2	(0.0–15.2)
Chlorhexidine digluconate (a)	0.5	2/78	2.6	(0.3–9.0)	1.4	(0.0–3.5)
Cocamidopropyl betaine	1.0	2/78	2.6	(0.3–9.0)	1.4	(0.0–3.5)
Amerchol L-101	50	2/78	2.6	(0.3–9.0)	1.4	(0.0–3.5)
Fragrance-mix	8.00	4/77	5.2	(1.4–12.8)	6.8	(0.0–15.8)
Fragrance-mix II	14.00	2/40	5.0	(0.6–16.9)	2.8	(0.0–7.0)
Myroxylon Pereirae resin (Balsam of Peru)	25.00	8/77	10.4	(4.6–19.4)	13.1	(2.6–23.6)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (e.g. Lyrall™)	5.00	3/78	3.8	(0.8–10.8)	1.9	(0.0–4.2)
Oak moss	1	2/75	2.7	(0.3–9.3)	1.4	(0.0–3.5)
Isoeugenol	1	2/76	2.6	(0.3–9.2)	6.8	(0.0–18.3)

All allergens in petrolatum, except where indicated: (a) in water.

The fragrance mix II was included to the standard series midterm in the study period, hence the lower number of patients tested.

Positive (+ to +++ patch test reactions).

Table 2 Results of threshold testing with SLS at three concentrations (0.25%, 0.5%, 1%) in water. Negative and questionable reactions ('neg./?') vs. at least weak positive reactions ('≥ weak pos.') combined

SLS concentration	0.25%	0.5%	1.0%	% of 77 patients
Reaction pattern	neg./?	neg./?	neg./?	19.5
	neg./?	neg./?	≥ weak pos.	39.0
	neg./?	≥ weak pos.		24.6
	≥ weak pos.			16.9

Only one strong positive reaction was observed, 6 patients (7.8%) tested completely negative.

cofactors worsening the skin condition revealed UV light in five cases; humidity, dust, dryness in two cases each; and heat and mechanical alteration in one patient each and 'other factors' in five subjects.

Skin susceptibility, defined as a visible skin reaction to SLS, was investigated following a standardized procedure with three different SLS concentrations in each patient. Most of the rosacea patients had at least questionable reactions; 6 patients (7.8%) tested completely negative,

and only one strong positive reaction was observed (see Table 2). Considering the lowest SLS concentration, 54 of 77 displayed at least a slight reaction (70.1%; exact 95% CI: 58.6–80.0%).

Discussion

This prospective study investigated rosacea patients with regard to additional allergic contact dermatitis, which has been discussed as one of the trigger factors of this inflammatory skin disease without having been adequately examined. Therefore, this investigation has been performed population related, in terms of targeting the subgroup of rosacea patients in the general population who were referred to the outpatient clinic of the Dermatology Department, University of Heidelberg. In 49 of the 78 cases, contact allergy was observed. The typical pattern of positive patch test reactions in rosacea patients is partially related to the particular age distribution²³ – in accordance with the late onset of rosacea. As has been observed previously,¹⁶ many of the most common contact allergens, like the ingredients of fragrance mix, are widespread used constituents in different topical formulations. Rosacea patients are exposed to a variety of topical formulations usually containing preservatives

and perfumes. Moreover, inflammation is prevailing, and therefore, these patients may be prone to develop contact sensitizations of the face.^{24–26} Although the precision of prevalence estimates is limited in our study due to its small size, a comparison with other population-related studies is interesting:

In a prevalence study of contact sensitization to fragrances on 100 'randomly selected female rosacea patients, 17 of 100 were positive for fragrance mix and/or its components (17%, exact 95% CI: 10.2–25.8%).²⁷ Although this percentage is higher – possibly due to the focus on females, who have a higher risk of fragrance allergy²⁸ – this difference to our results in males and females is not significant. In Germany, one population-related cross-sectional study on the prevalence of contact sensitization, also employing day 3 patch test readings, had been performed in a very similar age-segment (i.e. the KORA Study embedded in the MONICA Study).²⁹ Hence, sensitization prevalences are not confounded by a differing age (and sex) distribution and thus roughly comparable. Interestingly, sensitization to fragrance mix was much less common in our present study.^{29,30} Whereas in the just slightly younger (age median 51 years vs. 60 years in our study) KORA/MONICA sample, the prevalence of contact allergy to the fragrance mix amounted to 11.4% (95% CI: 10.4–12.4%), the crude prevalence was 5.2% (95% CI: 1.4–12.8%) in our study. This difference is not significant (cf. overlapping CIs); however, the periods of analysis were different, and the IVDK has noticed a general decrease in sensitization to fragrance mix I.³¹ In two other studies, however, sensitization to the fragrance mix I ranged between 1% and 2%,^{32,33} showing at least a tendency to higher proportions in rosacea patients. In contrast, a significantly higher proportion of contact allergy to MPR (Balsam of Peru) has been observed in our study [10.4% (4.6–19.4%) vs. 2.4% (1.9–2.9%) in the KORA/MONICA sample], which may warrant further, confirmative investigation and analysis of possible exposures – especially as MPR itself is not used in fragrances.³⁴ Sensitization to allergens of the standard patch test allergens in the present study compared with the general population was similar for neomycin sulphate, cobalt (II)-chloride, propolis and paraben mix.²⁹

Patients' own products rarely tested positive. No contact sensitization to first-line treatment topical antibiotics, erythromycin and metronidazole, were detected with either patients' own products or a particularly prepared patch test substance. This is most probably due to their low sensitizing potential. Erythromycin only rarely seems to cause contact allergy in rosacea.¹⁰ Metronidazole is a widely used synthetic antiprotozoal and antibacterial agent and generally well tolerated. Rarely, metronidazole gel may induce sensations like burning, stinging, redness, irritation, itching and even worsening of rosacea. True

allergic contact dermatitis due to topically applied metronidazole is extremely rare^{7,11,35} as confirmed by our retrospective¹⁶ as well as prospective data.

Gentamicin and framycetin sulphate, two other commonly used topical antibiotics, are not tested in the standard series. Thus, no population-related data in a strict sense is available for comparison. However, recently, the Clinical Epidemiology and Drug Utilization Research (CE-DUR) approach,³³ indirectly estimating contact sensitization frequency on the population level, has been extended to other topical therapeutic agents.³⁶ Although the CE-DUR incidence estimates are not directly comparable with our prevalence estimates, it is apparent that, on the population level, the prevalence of contact sensitization to topical aminoglycoside is well below 0.5%³⁶ (i.e. considerably lower than in the present study). These two antibiotics are not used for the topical therapy of rosacea;³⁷ therefore, the source of sensitization remains unclear. However, as the study patients did not suffer from venous leg ulcers/leg dermatitis, it can be hypothesized that gentamicin might have been applied as treatment for ocular symptoms associated with rosacea. This could explain most conclusively the unusually high rate of sensitization to these topical antibiotics in rosacea patients.

Additionally, a number of irritant patch test reactions were observed, caused by patient's own products, the clinical importance of these reactions in rosacea remaining unclear. As rosacea is accompanied by skin irritability, SLS tests have been performed in all study patients. Although there was only one patient with a strong reaction to SLS, there were many questionable/weak reactions in most patients, and only six were completely negative. Interestingly, the proportion of rosacea patients reacting at least slightly to the lowest SLS concentration, which is considered more discriminative than the higher concentrations, was significantly higher [54 of 77 (70.1%; exact 95% CI: 58.6–80.0%)] than the proportion observed in a previous large reference study (24.8%; 95% CI: 23.6–26.1%).³⁸ The different age distribution probably does not confound this comparison, as age is only weakly associated with SLS reactivity.³⁹ The main phenomenon detected by the SLS test is non-specific hyperirritability of the skin, which apparently does not only apply to different subgroups of eczema, but also to rosacea, as indicated by our results.

This is, to the best of our knowledge, the first prospective study on contact sensitization in rosacea patients. The investigation was not biased by just enrolling individuals with suspected allergic contact dermatitis. As a weak point, the size of the clinical sample was limited, and, with it, the precision of the prevalence estimates. We conclude that (i) allergic or irritant contact dermatitis does develop in rosacea patients, and (ii) a few of the observed allergens

may be related to morbidity-specific exposures. Therefore, diagnostic allergy tests are recommended in cases of doubt (i.e., apparent deterioration of rosacea following the use of skin care products or topical treatments). Diagnostic sensitivity will increase if topical treatments, cosmetics or perfumes used by the patients are tested in addition to commercial allergens. The role of pre-existing inflammatory skin diseases in sensitization and elicitation of contact allergy seems to be supported by our results. It is well known for a long time that general hyperirritability caused by pre-existing or persistent (local) eczema (also non-allergic of origin like leg dermatitis) facilitates sensitization and elicitation in a non-specific manner. This observation was finally substantiated with the 'danger model' on a molecular level.¹⁵ For the first time, it was shown that rosacea also may be such an unspecific trigger factor enhancing susceptibility for contact allergy.

Acknowledgement

We would like to thank Andrea Naumann und Jeannette Klemm-Wessbecher, Department of Dermatology, University of Heidelberg, for their invaluable technical assistance.

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