

## ORIGINAL ARTICLE

# Contact allergy to corticosteroids and *Malassezia furfur* in seborrhoeic dermatitis patients

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**Abstract**

**Background** Seborrhoeic dermatitis (SD) is a chronic skin disease, requiring long-term treatment, which might promote sensitization. *Malassezia furfur* (Mf) plays an important role in seborrhoeic dermatitis.

**Objectives** The aim of this study was to determine the frequency of contact sensitivity in SD patients.

**Patients and methods** A total of 100 patients and 20 healthy controls (HC) were investigated: 50 suffering from SD with no previous local corticosteroid treatment (SDN), 50 SD patients treated with local corticosteroids (SDC). Mycological examination for Mf was performed. All patients were patch tested with the baseline standard, corticosteroid series, with 12 commercial corticosteroid preparations frequently used in Croatia; and also with Mf.

**Results** *Malassezia furfur* was found in 44 (88%) SDN, 37 (74%) SDC, and in 4 (20%) HC; patch test reaction to Mf was positive in one SDN and in three SDC. Positive patch tests to standard allergens were observed in 17 (34%) SDN, 33 (66%) SDC and 2 (10%) HC. Patch tests to the corticosteroid series revealed positive reactions in 4 SDC and to commercial corticosteroids in seven patients, i.e. 2 SD and 5 SDC.

**Conclusions** Patch tests to the baseline series and to both individual corticosteroid and commercial corticosteroid preparations should be performed in SD patients with persistent dermatitis, as contact-allergic reactions may complicate their dermatitis. Sensitization to Mf was found to be infrequent.

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**Keywords**contact allergy, corticosteroid, *Malassezia furfur*, seborrhoeic dermatitis; patch testing**Conflicts of interest**

None declared.

**Introduction**

During the past decade, the reported incidence of allergic reactions to local corticosteroids has increased significantly. The diagnosis remains difficult, as the anti-inflammatory activity of the corticosteroid often leads to an unspecific clinical picture. Moreover, the symptoms are often mixed with those of an underlying skin disease, often a long-standing dermatitis that fails to respond to, or worsens after, corticosteroid application.<sup>1</sup>

Seborrhoeic dermatitis is an example of such a chronic skin disease, requiring long-term treatment that might promote sensitization. *Malassezia furfur* (Mf) is dimorphic lipophilic yeast that forms part of the normal human cutaneous microflora. SD is a multifactorial disease that needs endogenous and exogenous predisposing factors for its development. The pathogenesis and exact mechanisms through which this yeast causes inflammation are still not fully elucidated. It is hypothesized that the pathogenesis of SD

has an immune component, which is supported by the increased incidence in patients with immunosuppressive disorders. There are no data in the literature on contact sensibility to Mf in SD patients.

The aim of our study was to determine the frequency of contact sensitivity, to corticosteroids in particular, when patch-testing SD patients.

**Patients and methods**

We investigated 100 patients: 50 SD patients with no previous local corticosteroid treatment (SDN) (10 male and 40 female patients) and 50 SD patients treated with local corticosteroids (SDC) over a period from 1 month to more than 1 year (10 male and 40 female patients), as well as 20 healthy controls (HC) (5 men and 15 women). In total, there were 25 men and 95 women with the mean age of 45 years and age range 11–83 years.

A clinical diagnosis of SD was performed based on a history of waxing and waning severity and by the distribution of involvement upon examination. All investigated patients had a severe clinical picture of SD that involved scalp, eyebrows, nasolabial folds, cheeks, ears and in some patients even presternal region. The duration of dermatitis ranged from few years to over 10 years. Although all SD patients had a severe clinical picture, 50 of them claimed that they had never used topical corticosteroids (SDN). SDN patients were using local neutral and antimicrobial creams, while SDC patients were using local neutral, antimicrobial and corticosteroid creams.

Mycological examination for the Mf was performed with the help of a sterile scalpel, using skin scrapings from the nasolabial fold, supraorbital area and dorsal side of the nose. Samples were placed on a clean microscopic slide, a drop of 10% KOH was added and covered with a cover slip.

Patch tests were carried out in all 100 SD patients and in 20 HC with the baseline series (Table 1), obtained from the manufacturer Immunological Institute (Zagreb, Croatia); a corticosteroid series (Table 2), obtained from Chemotechnique Diagnostics (Vellinge, Sweden); and a panel of the 12 commercial corticosteroid preparations most frequently used in Croatia (tested as is). The panel included seven local corticosteroids, three corticosteroid-antibiotic

**Table 1** Positive patch test reactions to standard panel

| Standard allergen panel           |                      |            | Number of positive reactions |     |    |
|-----------------------------------|----------------------|------------|------------------------------|-----|----|
|                                   |                      |            | SDN                          | SDC | HC |
| 1.                                | Potassium dichromate | 0.5% pet.  | 0                            | 1   | 0  |
| 2.                                | Cobalt chloride      | 1.0% pet.  | 6                            | 5   | 0  |
| 3.                                | Nickel sulphate      | 5.0% pet.  | 7                            | 9   | 2  |
| 4.                                | Formaldehyde         | 1.0% aq.   | 0                            | 0   | 0  |
| 5.                                | Paraphenylenediamine | 0.5% pet.  | 0                            | 3   | 0  |
| 6.                                | Balsam of Peru       | 25.0% pet. | 3                            | 4   | 0  |
| 7.                                | Epoxy resin          | 1.0% pet.  | 1                            | 1   | 0  |
| 8.                                | Colophonium          | 20.0% pet. | 1                            | 1   | 0  |
| 9.                                | Mercury precipitate  | 10.0% pet. | 2                            | 3   | 0  |
| 10.                               | Benzocaine           | 5.0% pet.  | 2                            | 1   | 0  |
| 11.                               | Carba mix            | 3.0% pet.  | 7                            | 6   | 0  |
| 12.                               | Mercapto mix         | 2.0% pet.  | 1                            | 1   | 0  |
| 13.                               | Black rubber mix     | 0.6% pet.  | 0                            | 2   | 0  |
| 14.                               | Fragrance mix        | 8.0% pet.  | 2                            | 3   | 0  |
| 15.                               | Thiuram mix          | 1.0% pet.  | 1                            | 1   | 0  |
| 16.                               | Wood tars            | 12.0% pet. | 2                            | 2   | 0  |
| 17.                               | Paraben mix          | 15.0% pet. | 1                            | 0   | 0  |
| 18.                               | Neomycin sulphate    | 20.0% pet. | 2                            | 6   | 0  |
| 19.                               | Quaternium-15        | 1.0% pet.  | 1                            | 2   | 0  |
| 20.                               | Thimerosal           | 0.1% pet.  | 2                            | 3   | 0  |
| Total of positive reactions (=97) |                      |            | 41                           | 54  | 2  |

pet., petrolatum; aq., aqueous; HC, healthy controls; SDN, seborrhoeic dermatitis patients with no previous local corticosteroid treatment; SDC, seborrhoeic dermatitis patients who had used local corticosteroids.

**Table 2** Positive patch test reactions to the corticosteroid series

| Corticosteroid series             |                            |            | SDC |
|-----------------------------------|----------------------------|------------|-----|
| 1.                                | Amcinonide                 | 0.1% eth.  | 1   |
| 2.                                | Betamethasone-17-valerate  | 0.12% eth. | 3   |
| 3.                                | Clobetasol-17-propionate   | 0.25% eth. | 2   |
| 4.                                | Hydrocortisone             | 0.1% eth.  | 0   |
| 5.                                | Hydrocortisone-17-butyrate | 1% eth.    | 2   |
| 6.                                | Triamcinolone acetonide    | 0.1% eth.  | 0   |
| 7.                                | Budesonide                 | 0.1% eth.  | 2   |
| 8.                                | Prednisone                 | 1% eth.    | 0   |
| 9.                                | Tixocortol-21-pivalate     | 0.1% pet.  | 2   |
| Total of positive reactions (=12) |                            |            | 12  |

pet., petrolatum; eth., ethanol; SDC, seborrhoeic dermatitis patients who had used local corticosteroids.

combinations and two corticosteroid-keratolytic agent combination (Table 3). The yeast Mf was patch tested using the water-soluble extract of Mf with protein concentration of 5 mg/mL,

**Table 3** Positive patch test reactions to the commercial corticosteroid panel

| Commercial corticosteroid panel                                                          | Number of positive reactions |     |    |
|------------------------------------------------------------------------------------------|------------------------------|-----|----|
|                                                                                          | SDN                          | SDC | HC |
| Advantan® (methylprednisolone aceponate) cream (Bayer d.o.o., Zagreb, Croatia)           | 0                            | 1   | 0  |
| Afloderm® (acemetasone dipropionate) cream (Belupo, Koprivnica, Croatia)                 | 0                            | 2   | 0  |
| Beloderm® (betamethasone dipropionate) cream (Belupo)                                    | 0                            | 2   | 0  |
| Belogent® (betamethasone dipropionate +gentamicin) cream (Belupo)                        | 0                            | 0   | 0  |
| Belosalic® (betamethasone dipropionate + salicylic acid) (Belupo)                        | 0                            | 0   | 0  |
| Cutivate® (fluticasone propionate) cream (GlaxoSmithKline, Wellcome, UK)                 | 0                            | 0   | 0  |
| Dexamethasone-neomycin® (dexamethasone+neomycin) cream (Lek, Ljubljana, Slovenia)        | 2                            | 1   | 0  |
| Elocom® (mometasone furoate) cream (Schering-Plough, Kenilworth, NJ, USA)                | 0                            | 2   | 0  |
| Eumovate®/Dermovate® (clobetasone butyrate/propionate) cream (GlaxoSmithKline)           | 0                            | 0   | 0  |
| Fluacet® (fluocinonide) lotion (JGL, Rijeka, Hrvatska)                                   | 0                            | 0   | 0  |
| Geokorton® (hydrocortisone acetate + oxytetracycline) ointment (Pliva, Zagreb, Hrvatska) | 0                            | 1   | 0  |
| Locacorten® (flumetasone+salicylic acid) cream (Pliva)                                   | 0                            | 0   | 0  |
| Total of positive reactions (=11)                                                        | 2                            | 9   | 0  |

HC, healthy controls; SDN, seborrhoeic dermatitis patients with no previous local corticosteroid treatment; SDC, seborrhoeic dermatitis patients who had used local corticosteroids.

prepared by ALK Herholm, Denmark. The solution was applied on a patch of filter paper attached to an adhesive strip. Patch tests were performed using Finn Chambers on Scanpor tape left on the skin of the back for 2 days. The patch tests were read at Day 2 and 3, and also at day 7. Reactions were scored as recommended by the International Contact Dermatitis Research Group (ICDRG). All corticosteroids were tested in ethanol, except for tixocortol pivalate that was tested in petrolatum. Statistical methods used were chi-squared test and Z test.

## Results

According to the patient's history, of the 50 SDC patients 10 (20%) had used local corticosteroids for more than 1 year, 10 (20%) between 6 and 12 months, 16 (32%) between 1 and 6 months and 14 (28%) during less than a month.

Skin scrapings revealed Mf in 44 (88%) SDN, 37 (74%) SDC and in 4 (20%) HC. The difference between SDN and SDC groups was not statistically significant. The presence of the yeast in SDC group depended on the duration of corticosteroid use and was slightly decreased in patients treated for more than a year (Fig. 1). Patch test reaction to Mf was positive in only one (2%) SDN and in three (6%) SDC patients, whereas negative in the 20 HC.

Patch tests to the baseline series allergens (Table 1) were positive in 52 patients, some of whom showed multiple positive reactions: 17 (34%) SDN, 33 (66%) SDC and 2 (10%) HC. The difference between SDN and SDC groups was statistically significant ( $P = 0.00069$ ). Nickel sulphate was shown to be the most frequent allergen in both SDN and SDC groups (and the only positive allergen in the HC group), followed by carba mix, cobalt chloride and neomycin sulphate (Table 1). The SDC patients who had been treated with corticosteroids over a longer period presented more frequent positive reactions to allergens in the baseline series: over a year: 9 of 10; 6–12 months: all 10; 1 and 6 months: 13; under a month: 1 of 14 (Fig. 2). The result for the patients who were using corticosteroids less than a month is statistically significant compared with those in the other examined groups ( $P = 0.00000$ ).

Positive patch tests to the individual corticosteroids were observed in 4 (3%) SDC patients (Table 2), while the 50 SDN patients and 20 healthy controls remained completely negative. As

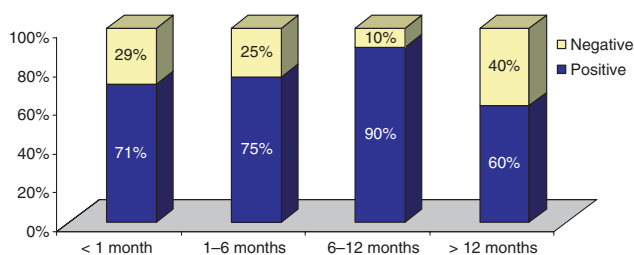


**Figure 1** The frequency of positive versus negative test results to the yeast *Malassezia furfur* in SDC patients in relation to the duration of local corticosteroid therapy.

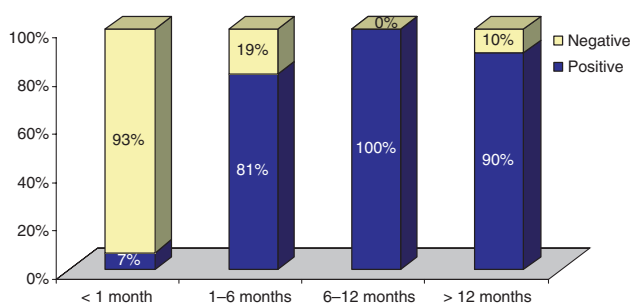


**Figure 2** Patch test results to allergens from the baseline (standard) series in SDC patients in relation to the duration of local corticosteroid usage.

tixocortol 21-pivalate is not commercially available in Croatia, allergic patients had not been exposed to this molecule and the positive reactions to it are attributed to cross-sensitivity. Patch tests to the commercial corticosteroid panel revealed positive reactions in seven (6.0%) patients, i.e. two SDN and five SDC (Table 3). The two SDN patients who reacted positively to Dexamethasone + Neomycin® (LEK, Ljubljana, Slovenia) cream presented with a contact allergy to neomycin in the baseline series. Four SDC patients presented with multiple positive reactions to individual corticosteroids (two to 2 and two to 4 corticosteroids, with three of them also reacting to commercial preparations (two to 2, and one to 1 of such preparations) (Tables 2 and 3). In all four patients, a true cross-reaction was found.

## Discussion

Half (50%) of the SDN patients reacted positively to allergens from the baseline series, while SDC presented positive patch test reactions more frequently than the SDN group. The frequency increased with the length of the corticosteroid application period. Patients who were using corticosteroids showed statistically significantly more positive reactions to the baseline series of allergens ( $P = 0.00069$ ). Despite being the most frequent allergen, nickel sulphate was not considered relevant. Positive reactions to neomycin sulphate, Balsam of Peru were considered relevant because those patients had been using creams that contained those allergens. Besides local corticosteroids, SDC patients used other topical creams and ointments, and developed multiple sensitizations to allergens in the baseline series, such as Balsam of Peru, fragrances mix and neomycin. Some patients, besides their corticosteroid hypersensitivity, also developed signs of perioral, centrofacial or diffuse steroid dermatitis, including steroid acne.<sup>2</sup>

Although 10 of 50 SDC complained of worsening of their dermatitis during corticosteroid application, patch tests to corticosteroids detected allergy in only six of them. In all SDC patients who had positive patch test reaction to corticosteroids, SD improved following the advice they got upon patch test.

Some of the patients also showed multiple positive test reactions: nine SDN patients reacted to three or more standard

allergens and two SDC presented up to four positive reactions in the corticosteroid panel. One of the reasons might be that these patients have used large numbers of corticosteroids and would thus be vulnerable to concomitant sensitization.<sup>1</sup>

Chronic dermatitis such as facial eczema is indeed a risk factor for the development of (multiple) sensitization, particularly to topical pharmaceutical products such as corticosteroids.<sup>3,4</sup> Corticosteroid-allergic patients frequently exhibit multiple reactions to local corticosteroids, including those they have never used,<sup>5</sup> which strongly suggests cross-reactivity. To avoid testing with many corticosteroids, screening agents are being used, i.e. tixocortol pivalate and budesonide. Boffa *et al.* found the combination of both to be able to identify 91.3% of corticosteroid allergic subjects<sup>6</sup> and that at least 90% of individuals with a reaction on patch testing to budesonide are allergic to another corticosteroid.

Two SDC patients did not react to the individual corticosteroid series, but showed positive patch test reactions to commercial corticosteroid preparations. Some authors<sup>7</sup> argue that patch testing with the patient's corticosteroid in the commercial cream base yields more positive results than patch testing with the commercial corticosteroid ointment base, or with the pure corticosteroid in either petrolatum or in alcohol. This was confirmed in our limited study. Commercial preparations of corticosteroids may contain vehicles that increase skin penetration and bioavailability.<sup>8</sup> However, it must be borne in mind that any ingredient of a corticosteroid preparation, active principles (for example neomycin in two of our cases) as well as the vehicle, may be the allergenic culprit.<sup>9</sup>

Our study showed that the corticosteroids previously reported as extremely rare sensitizers<sup>10</sup> (such as bethamethasone valerate in the corticoid series as well as bethamethasone-dipropionate and mometasone-furoate containing preparations) most frequently elicited positive reactions. Thus, in contrast to the current clinical practice in Croatia, these potent corticosteroids should not be used to treat SD.

False-negative or doubtful patch test reactions to corticosteroids may occur because of the corticosteroid anti-inflammatory effect, the pharmacological effects of vasoconstriction and vasodilatation, and the edge effect.<sup>1,8</sup> We observed this phenomenon in five of our patients. Moreover, one of our patients patch tested with corticosteroids reacted negatively at the first reading and become positive at the second reading; and two of the initially negative patients exhibited a positive reaction on day 7. According to a study of Isaksson *et al.* 30% of contact allergic reaction to corticosteroids may be missed if 7-day (late) reading had not taken place.<sup>11,12</sup>

Skin scrapings and mycological analysis<sup>13,14</sup> have shown that patients with SD usually carry an increased number of Mf compared with SD-free individuals. The exact mechanism by which the skin lesions are induced remains unknown. Moreover, the yeast can also be found in healthy controls. Positive patch test reactions to Mf are frequently observed in atopic dermatitis and less frequently in SD patients.<sup>15–17</sup> In our study,

a positive reaction was found in one SDN and in three SDC; all four patients were suffering from frequent recurrences of their dermatitis.

The influence of local corticosteroids on Mf is not clear. A study<sup>18</sup> comparing treatments of the scalp SD with an antimycotic agent (2% miconazole), a corticosteroid (1% hydrocortisone) and a combination of both found that the yeast count was the lowest in the group of patients treated with the antimycotic and the highest in those treated with hydrocortisone. After 3 months of therapy, the yeast count was still the highest in the corticosteroid group. Similar results, showing an increased presence of the yeast after applying corticosteroids, were also observed in other studies.<sup>19,20</sup> These findings contrast with our data showing the yeast count being smaller in SDC group, although not highly statistically significant ( $P = 0.03718$ ) (controls were 50 SDN patients using antimycotic and neutral creams only). We found a peak incidence (90%) in SDC who had used corticosteroids between 6 months and 1 year and a lower incidence (40%) in SDC who had used corticosteroids for more than a year (Fig. 1). Data describing a decrease in the Mf count after prolonged (more than 1 year) corticosteroid usage were not reported.

## Conclusion

Our study also showed that SD patients may also suffer from contact-allergic reactions to several allergens of the baseline series, and also to corticosteroids, which may complicate the clinical picture. According to our study, contact sensitivity is more frequent in patients previously applied corticosteroids for SD. When the eczematous lesions do not respond properly to corticosteroid treatment, patch testing with the commercial products used and their ingredients should be performed.

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