

Dermatologic and ocular diseases

Trichophyton-specific IgE in patients with dermatophytosis is not associated with aeroallergen sensitivity

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Background: It has been proposed that *Trichophyton* infection is associated with atopy and allergy.

Objectives: Our purpose was (1) to confirm whether atopy predisposes to chronic dermatophytosis and (2) to investigate whether *Trichophyton* infection induces atopic disease.

Methods: Patients attending dermatology clinics and suspected of having dermatomycosis underwent in a prospective manner fungal culture and *Trichophyton* and inhalant skin tests, and blood serum was collected for total IgE and *Trichophyton* radioallergosorbent testing. Personal and family history of atopic diseases was also investigated.

Results: According to mycologic culture, atopic history, and inhalant skin test results, patients were classified into 4 groups: (1) atopy plus mycosis (n = 28), (2) atopy (n = 26), (3) mycosis (n = 35), and (4) no atopy, no mycosis (n = 33). Patients with active mycosis (groups 1 and 3) demonstrated significantly increased positivity of *Trichophyton* skin tests compared with patients without fungal infection (groups 2 and 4), regardless of their atopic status, whereas atopic patients (those in groups 1 and 2) had significantly increased levels of total serum IgE compared with nonatopic subjects. Trichophytosis was not more prevalent in atopic than in nonatopic subjects, and atopic diseases were not more frequent in culture-positive than in culture-negative patients.

Conclusions: Our results indicate that *Trichophyton*-specific IgE is observed in patients with trichophytosis regardless of atopy. (J Allergy Clin Immunol 2000;105:547-51.)

Key words: Atopy, dermatophytosis, *Trichophyton*, IgE, radioallergosorbent test

Dermatophytoses are skin fungal infections commonly found in the population; fungal products are able to penetrate into the skin to induce an immune and eczema-

Abbreviations used

DTH:	Delayed-type hypersensitivity
IH:	Immediate hypersensitivity
RAST:	Radioimmunosorbent test
TM:	<i>Trichophyton mentagrophytes</i>
TR:	<i>Trichophyton rubrum</i>

tous response.¹ *Trichophyton* is the genera most frequently observed, and most patients have a self-limited disease that is controlled by cell-mediated immunity.²⁻⁹ A chronic recalcitrant disease is observed in patients with decreased cellular immunity.¹⁰

In atopic patients and in those with IgE antibodies to *Trichophyton* antigens (demonstrated by immediate-type [IH] skin tests or immunoassays), an increased prevalence of chronic trichophytosis has been suggested.¹¹⁻¹³ Because *Trichophyton* antigens are able to induce both IH and delayed-type hypersensitivity (DTH), it has been proposed that trichophytosis could represent an interesting model for studying the dichotomy between IH and DTH and the T_H1/T_H2 polarization observed in a number of human diseases.^{14,15}

A few years ago some authors proposed the existence of an association between chronic dermatophytosis and atopy.^{3,5,10,16,17} The association of allergic rhinitis or asthma, chronic noninflammatory tinea infections, increased IgE, *Trichophyton*-specific IgE antibodies, IH, and reduced DTH to *Trichophyton* encouraged Jones⁴ to propose an "atopic-chronic dermatophytosis syndrome" with the hypothesis that in patients with IH to *Trichophyton* persistent absorption of dermatophyte antigen could give rise to inflammation of bronchi or nasal passages. According to this author and to Hay and Brostoff,¹⁷ atopy could also represent a risk factor for chronic dermatophytosis. However, the last proposal was challenged later on by Kaaman.¹⁸

More recently, Braunstein Wilson et al¹⁹ reported about an atopic patient who had *Tinea unguium* infection, IH, and specific IgE and IgG antibodies to *Trichophyton* and recalcitrant hand and foot eczema. Interestingly, the eczematous lesions resolved after systemic antifungal therapy. They proposed that atopic eczema in this patient was exacerbated by chronic dermatophyte infection and

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Trichophyton hypersensitivity. The same group observed a patient with severe asthma, tinea pedis and cruris, and IH plus positive radioallergosorbent test (RAST) to *Trichophyton* whose asthma improved with antifungal therapy.²⁰ Furthermore, other studies have suggested a relationship of *Trichophyton* infection to other allergic diseases such as urticaria/angioedema, asthma (mostly intrinsic), and rhinitis.^{3,21-25}

Ward et al¹³ could demonstrate, by means of nasal and bronchial challenges, that *Trichophyton* antigens may indeed cause rhinitis and asthma symptoms. This observation confirms the reports of IH and rhinitis and asthma manifestations that appear in podiatrists after occupational inhalation of *Trichophyton* proteins from nail dust while grinding infected nails.²⁶ In regard to these observations, it must be said that most studies have focused on selected allergic populations.

The purpose of our investigation was 2-fold: (1) to study the prevalence of the atopic trait and atopic diseases in patients with dermatophytosis and (2) to study IgE responses to *Trichophyton* antigens in patients with trichophytosis and in controls.

METHODS

Patients

Individuals with suspected dermatomycosis attending dermatology outpatient clinics of Centro Médico "Dr Carlos Diez del Ciervo" and Hospital "Dr Miguel Pérez Carreño" were prospectively admitted in the study after giving written informed consent. Clinical information about age, sex, and personal and family history of asthma, rhinitis, atopic dermatitis, urticaria, food, and insect or drug allergies was obtained by direct questioning. Duration and localization of skin lesions were also registered. The protocol was approved by the Postgraduate Education Board, Faculty of Medicine, Universidad Central de Venezuela.

Skin tests

IH skin tests were carried out by the prick method with readings at 15 minutes, when wheal diameters were measured. Negative (glycerosaline solution) and positive (1% histamine phosphate) controls were simultaneously applied in the forearm. Because there is a low frequency of aeroallergen (pollen) sensitivity in Caracas, only *Dermatophagoides farinae* and cockroach extracts were tested as inhalant allergens. *D farinae* was obtained from Center Laboratories (Port Washington, NY). Cockroach (*Periplaneta americana*) extract was purchased from Antigen Laboratories (Liberty, Mo). *Trichophyton* extracts for intradermal tests from Bayer (New York, NY) were also applied. According to the manufacturer, Bayer extract is a mixture of *Trichophyton rubrum* (TR), *Trichophyton mentagrophytes* (TM), and *Trichophyton tonsurans*. For prick tests, wheals greater than the glycerosaline control by 3 mm or more were considered as positive. For the intradermal route, wheals 5 mm or more than negative control were regarded as positive.

Serum IgE and RAST

Blood from antecubital veins was obtained simultaneously with mycologic cultures, and after separation sera were kept at -70°C until processing. Total serum IgE was measured by ELISA with a commercial kit (Kallestad Total IgE Microplate, Sanofi Diagnostics Pasteur, Chaska, Minn). Results were expressed in kilounits per liter. RAST for TR and TM was done at the Allergy Testing Laboratory, Gainesville, Fla. Results are presented as counts per minute.

Definition of atopy

A patient was considered as atopic if a positive skin test to mite or cockroach was present together with a personal or family history (first-degree relatives [ie, parents or siblings]) of rhinitis, asthma, or atopic dermatitis.

Mycologic studies

Standard methods for dermatophyte culture in Sabouraud's medium, as described by Borelli,²⁷ were used. Lesion samples were obtained by means of sterile surgical knife scratching and were also observed directly in the microscope after clarification with 10% potassium hydroxide.

Statistical analysis

Statistical comparisons were performed by means of the Student *t* test, and data were expressed as the mean $\pm$ 1 SD. For significance, *P* values less than .05 were taken into account. To compare atopy and asthma prevalence proportions, the chi-square test was used.

RESULTS

Demographics

One hundred twenty-two subjects were admitted into this study. Sixty-three of them had positive fungal cultures (TR, 37; TM, 24; *Trichophyton* spp, 2). Five additional patients had *Epidermophyton floccosum* infection and were not included in the analysis. Fifty-nine patients had negative cultures. Prick tests with *D farinae* or cockroach extracts were positive in 54 patients and negative in 68.

According to the results of inhalant prick tests, family and personal atopic history, and culture results, patients were classified in 4 groups as follows: group 1, atopy plus mycosis (*n* = 28), TR 19, TM 7, *Trichophyton* spp 2; group 2, atopy (*n* = 26); group 3, mycosis (*n* = 35), TR 18, TM 17; and group 4, no atopy, no mycosis (*n* = 33).

Age and sex distribution and the frequency of atopic history are presented in Table I. Mycotic lesions were present in the feet (group 1, 20 patients; group 3, 24 patients), foot skin and nails (group 1, 5 patients; group 3, 11 patients), nails exclusively (group 1, 2 patients), and hands (group 1, 1 patient). The mean duration of mycosis was 23.7 ± 40.6 months for group 1 and 36.6 ± 58.7 months for group 3 (not significant).

IH to *Trichophyton*

Results of intradermal tests are shown in Fig 1. Mean wheal diameters were significantly higher in patients from groups 1 and 3 than in patients from groups 2 and 4 (*P* < .05), and no significant differences between groups 1 and 3 were present.

Percentages of skin test positivity (wheals 5 mm greater than glycerosaline control) were significantly higher in patients from groups 1 and 3 than in those from groups 2 and 4. No significant differences in skin test diameters were present for groups 1 and 3 when they were compared between patients with cultures positive for TR and those positive for TM.

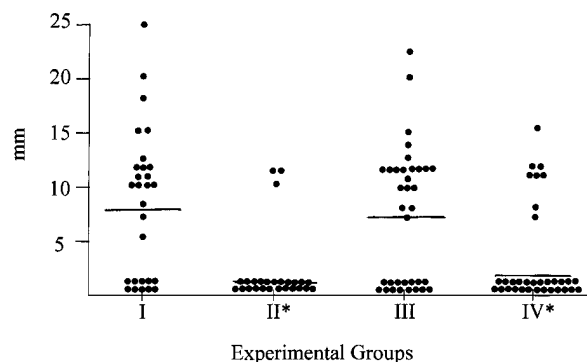


FIG 1. Results of intradermal immediate-type skin tests with *Trichophyton* antigen. Group 1, Atopy + mycosis. Group 2, Atopy. Group 3, Mycosis. Group 4, No atopy, no mycosis. Horizontal lines, Mean values. Asterisk, $P < .05$.

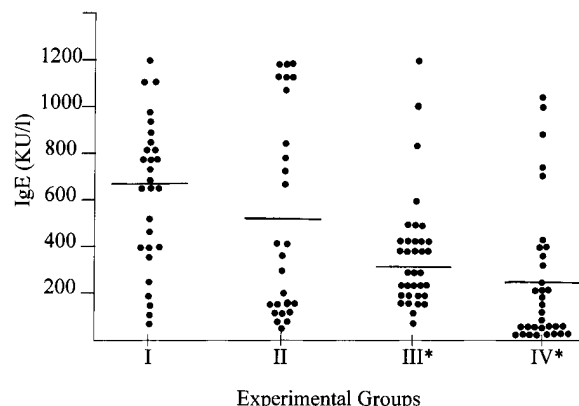


FIG 2. Total serum IgE in patients and controls. Group 1, Atopy + mycosis. Group 2, Atopy. Group 3, Mycosis. Group 4, No atopy, no mycosis. Horizontal lines, Mean values. Asterisk, $P < .05$.

TABLE I. Demographics

	No.	Age (y)	Male	Female	Asthma	Rhinitis	AD	Drugs	Food	Insects	Urticaria
Group											
1	28	26.6 ± 10.7	21	7	20	14	2	1	1	2	1
2	26	29.5 ± 10.5	14	12	17	10	8	5	1	0	0
3	35	31.1 ± 12.2	27	8	0	0	0	0	0	0	0
4	33	27.0 ± 11.0	24	9	0	0	0	0	0	0	0
Total	122	28.1 ± 10.2	86	36	37	24	10	6	2	2	1

AD, Atopic dermatitis.

RAST

TR RAST results were as follows: group 1, 1639.5 ± 2374 counts/min; group 2, 820.7 ± 966 counts/min; group 3, 906.3 ± 1112 counts/min; and group 4, 506.0 ± 527 counts/min. There were no significant differences between groups 1 and 2, 1 and 3, 2 and 3, 2 and 4, and 3 and 4. The only significant difference was between groups 1 and 4 ($P = .01$).

TM RAST results were as follows: group 1, 3627.6 ± 5618 counts/min; group 2, 1321.6 ± 2362 counts/min; group 3, 1430.6 ± 2314 counts/min; and group 4, 585.1 ± 732 counts/min. Groups 2, 3, and 4 had significantly lower counts than group 1 did ($P < .05$), whereas no differences were present between groups 2 and 3 and groups 2 and 4. TM RAST results were significantly lower for group 4 than for group 3 ($P = .05$).

Total serum IgE

Serum IgE levels are presented in Fig 2. As depicted, IgE values were significantly lower in groups 3 and 4 compared with groups 1 and 2. No differences were observed when groups 1 and 2 and groups 3 and 4 were compared.

Atopy prevalence

An atopic history was present in 22 of 63 (34.9%) patients with positive fungal cultures and in 26 of 59 (44.0%) patients with negative cultures (not significant). Inhalant skin tests were positive in 31 of 63 (49.2%) cul-

ture-positive patients and in 29 of 59 (49.1%) culture-negative individuals (not significant).

Fungal cultures were positive in 28 of 54 (51.8%) subjects with atopic history plus positive inhalant skin tests and in 49 of 68 (72.0%) patients without atopy ($P = .02$). Culture-proved dermatomycosis was present in 31 of 59 (52.5%) patients with positive mite or cockroach prick tests and in 40 of 63 (63.4%) patients with negative inhalant skin test results (not significant) (Tables IIA and IIB). In summary, no correlation between atopy and trichophytosis was demonstrated, and no increased chronic dermatomycosis was evidenced in atopic subjects.

Thirty-seven patients (30.3%) had asthma history. From the 63 with positive fungal culture, 20 had asthma (31.7%), whereas of 59 patients with negative culture 17 (28.8%) were asthmatic (not significant).

Duration of dermatophytosis

According to the duration of the infection, culture-positive patients (groups 1 and 3) were classified into acute (infection lasting less than 6 months) and chronic (mycosis of more than 6 months) groups. Thirty-six patients had acute infection (mean 16.2 ± 5.8 weeks, range 2 to 24 weeks), and 27 had chronic infection (mean 9.8 ± 19.4 years, range 1 to 20 years). There were no statistically significant differences in the results of *Trichophyton* skin tests, RAST, total serum IgE levels, or atopy prevalence when data from acute and chronic cases were compared (data not shown).

TABLE IIA. Trichophytosis and atopy are independent clinical conditions: atopy prevalence according to culture result

Fungal culture	No.	Atopic history		Inhalant skin tests	
		Positive (%)	Statistical significance*	Positive (%)	Statistical significance
Positive	63	22 (34.9)	—	31 (49.2)	—
Negative	59	26 (44.0)	NS	29 (49.1)	NS

NS, Not significant.

*Chi-square test.

TABLE IIB. Trichophytosis and atopy are independent clinical conditions: fungal cultures according to atopic parameters

Atopic history	No.	Positive cultures (%)	Statistical significance*	Inhalant skin tests	No.	Positive cultures (%)	Statistical significance*
Positive	54	28 (51.8)	—	Positive	59	31 (52.5)	—
Negative	63	49 (72.0)	$P = .02$	Negative	63	40 (63.4)	NS

NS, Not significant.

*Chi-square test.

DISCUSSION

We have investigated two hypotheses: (1) that atopic patients are predisposed to the development of chronic trichophytosis and (2) that *Trichophyton* antigens are able to induce atopic disease. In spite of a number of studies supporting these proposals, our results do not permit us to corroborate any of those suggestions in our population because culture-proved chronic trichophytosis was equally seen in atopic and in nonatopic subjects, whereas atopic diseases and asthma were not more prevalent in patients with trichophytosis. In agreement with our results, Sorensen and Jones³ found that only a small proportion (6%) of patients with asthma have immediate hypersensitivity to *Trichophyton* and the prevalence is about 10% in adult asthmatic patients, whereas *Trichophyton* IH is observed more frequently in patients with chronic dermatophytosis without atopic dermatitis than in patients with chronic dermatophytosis and atopic eczema.¹² Ward et al²⁸ have stated that the association of “*Trichophyton* asthma” with atopy is 44%.

Furthermore, we observed that most patients with trichophytosis have *Trichophyton*-specific IgE antibodies, as shown by means of intradermal skin tests, in the absence of an allergic disease, which encourages us to propose that absorption of *Trichophyton* antigens through the skin would induce sensitization (specific IgE production) but not allergic disease, as previously suggested.²² This observation would indicate that there is something unique about *Trichophyton* antigens in that they specifically induce the production of specific IgE. The reasons for this kind of response are not known at the present time, but they might involve the nature of the antigen(s) or the route (cutaneous) and prolonged duration of the exposure.

In regard to *Trichophyton*-specific IgE, we obtained some interesting results. Positive intradermal skin tests to *Trichophyton* were more prevalent in patients with trichophytosis (groups 1 and 3) than in uninfected individuals. This might suggest that intradermal skin tests could be useful for the distinction between infected and unin-

fected patients, with better sensitivity, specificity, and predictive values than RAST. Because in this study as well as in other published studies²² there was a good statistical correlation between skin tests and RAST (data not shown), skin tests could be selected for diagnostic purposes instead of more expensive in vitro tests.

Our results suggest that there is no particular predisposition to develop chronic trichophytosis in atopic patients, and *Trichophyton* infection does not seem to be a frequent etiologic factor for atopic disease. *Trichophyton*-specific IgE is associated with active infection and may be useful for diagnosis in cases where mycologic techniques are not easily available.

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