

Short communication

Trichophyton sensitivity in allergic and nonallergic asthma

Background: Although the role of inhaled fungi in inducing asthma has been repeatedly confirmed, there are few reports about the association of asthma with dermatophyte sensitivity and the causal role of *Trichophyton* allergy in asthma. The objective was to investigate the presence of *Trichophyton* sensitivity among patients with allergic and nonallergic asthma in combination with tinea, and to compare the situation with several control groups in order to evaluate the factors determining *Trichophyton* sensitivity.

Methods: A total of 86 subjects (55 female, 31 male) with a mean age of 38.6 ± 11.1 years were included in the study. The patients were divided into five groups:

- 1) nonallergic asthma plus tinea ($n=19$)
- 2) allergic asthma plus tinea ($n=15$)
- 3) asthma without tinea ($n=22$)
- 4) tinea without asthma ($n=17$)
- 5) healthy controls ($n=13$).

Skin tests with standardized extracts of *T. rubrum* and specific IgE measurements were performed in all subjects. All patients were also subjected to microscopic evaluation and fungal culture for dermatophyte infection.

Results: The skin test positivity rate to *Trichophyton* extract of groups 1 (63.1%), 2 (46.7%), and 4 (47.1%) was higher than that in groups 3 (4.4%) and 5 (7.7%) ($P<0.05$). Although not significant, the rates of sensitivity to *T. rubrum* (63.1%) and of severe asthma (31.6%) were higher in the group with nonallergic asthma with tinea (group 1) than in other groups. Among 51 patients in whom direct microscopic evaluation revealed dermatophyte infection, 60.8% had positive fungal cultures for *T. rubrum* (58.1%), *T. mentagrophytes* (35.5%), and *Candida* (6.4%).

Conclusions: According to our data, the presence of fungal infection seems to be an important determinant in hypersensitivity to *Trichophyton* whether or not the subject is asthmatic and/or allergic. Since a greater proportion of patients with nonallergic asthma – in whom the rate of severe asthma was also higher – showed positive skin tests to *Trichophyton* extracts in this study, we believe that patients with severe, intrinsic asthma should be examined for signs of fungal infection and tested to determine immediate hypersensitivity to dermatophyte antigens.

**D. Mungan¹, S. Bavbek¹,
Y. Peksari², G. Çelik¹, E. Gürgey²,
Z. Mısırlıgil¹**

Departments of ¹Allergy and ²Dermatology, University of Ankara, Ankara, Turkey

Key words: asthma; tinea pedis; *Trichophyton* hypersensitivity.

Dr D. Mungan
Department of Allergy
University of Ankara
Ankara
Turkey

Accepted for publication 18 December 2000

The role of inhaled fungi in inducing asthma was first reported 100 years ago. However, the role of dermatophytes in asthma was first described in 1930 by Wise & Sulzberger (1) in a patient with asthma and severe tinea whose asthma improved with the treatment of the fungal infection. Subsequently, the association between dermatophyte infections and allergic diseases in patients with immediate hypersensitivity reactions to *Trichophyton* has been reported in several studies (2–9). Moreover, some encouraging reports suggest that antifungal treatment may improve the symptoms of asthma and reduce

the need for medication (2, 5). In a recent study, Ward et al. reported significant clinical improvement with fluconazole in patients with severe or moderately severe asthma (6).

There are various explanations of the contribution of dermatophyte antigens to the respiratory tract disease. It has been reported that some patients with severe fungal infection shed sufficient skin scales to create an airborne challenge, and podiatrists can be sensitized by exposure to *Trichophyton* allergens while grinding infected toenails (10). However, the most likely route of sensitization is

thought to be the absorption of *Trichophyton*-derived proteins from the infected area. Development of T-cell sensitization and production of IgE antibody are widely assumed to follow the absorption of the antigen (2, 4). Repeated attempts to grow this dermatophyte from nasal passages, sinuses, or lungs have been negative. Thus, it is suggested that if dermatophyte antigens contribute to the respiratory tract disease, the antigen must either be absorbed or become airborne (2–4). Many studies in the literature have dealt with the causal role of *Trichophyton* sensitivity in asthma. However, to date, the prevalence of *Trichophyton* sensitization has not been compared between, asthmatic and nonasthmatic individuals with chronic dermatophytosis. Our study aimed to investigate *Trichophyton* sensitivity in allergic and nonallergic asthmatics and nonasthmatic subjects with or without tinea, and to evaluate the factors determining *Trichophyton* allergy.

Material and methods

Subjects

A total of 86 subjects were included in the study, divided into the following groups:

- 1) *Patients with asthma*: randomly selected asthmatic patients from our outpatient clinic were recruited into the study. Asthma was diagnosed by clinical history and laboratory documentation of reversible airway obstruction (11). All asthmatic patients had been in the stable period of their disease for at least 1 month and were taking regular antiasthma medications. None of them were taking systemic corticosteroids, antihistamines, or mast-cell stabilizers. Asthma severity was assessed according to international guidelines (11). Asthmatic patients were divided into three groups: nonallergic asthmatics with tinea (group 1), allergic asthmatics with tinea (group 2), and asthmatic patients (either allergic or nonallergic) without dermatophytosis (group 3).
- 2) *Patients with tinea*: randomly selected subjects with tinea admitted to the dermatology clinic comprised group 4. They were included in the study before beginning antifungal treatment.
- 3) *Control group*: healthy subjects without asthma and tinea served as the control group of the study (group 5).

Characteristic features of the groups are shown in Table 1.

Skin tests

In the evaluation of atopy, skin prick tests (SPTs) were performed with a standardized panel (Stallergènes, France) of airborne allergens including grass, tree, and weed pollens; molds; *Dermatophagoides*

pteronyssinus and *D. farinae*; and cat and dog allergens. Histamine dihydrochloride (10 mg/ml) and glycerol diluent were used as positive and negative controls, respectively. A wheal size larger than 3 mm or greater than that produced by the control solution was considered a positive reaction.

In the evaluation of *Trichophyton* sensitivity, standardized extracts of *T. rubrum* (Stallergènes, France) were used. Prick tests were followed by intradermal tests (dilutions of 1/10 000 and 1/1000) if they were negative. Immediate reactions to *T. rubrum* were read at 15 min after the intradermal injections with an end point of a 7 × 7 mm or larger wheal.

In vitro tests

Specific IgE to *T. rubrum* was measured by the UniCAP system according to the manufacturer's instructions (Pharmacia, Sweden). Results equal to or greater than class II (IgE level of ≥ 0.7 kU/l) were considered positive.

Mycologic investigations

Tinea was localized in toe web spaces and/or toenails in the study groups. Direct microscopic examination of the material was performed in all subjects. Lesion samples were obtained by means of sterile surgical knife scratching and observed directly under the microscope after clarification with 10% potassium hydroxide. In cases with positive direct microscopy, *Trichophyton* species were cultured by standard methods for dermatophytes in Sabouraud's medium.

Statistics

Results were expressed as percentage of the patients, and differences in percentages between groups were measured by chi-square and Fisher's exact tests. Logistic regression analysis was used to determine the risk of having positive skin tests to *T. rubrum* in groups 1 and 2. A *P* value of less than 0.05 was considered significant. The Statistical Package for Social Sciences (SPSS) for Windows, Version 6.0, was used to analyze the data.

Results

Skin tests

The skin test positivity rates to *Trichophyton* extract of groups 1 (63.1%), 2 (46.7%), and 4 (47.1%) were higher than those for groups 3 (4.4%) and 5 (7.7%) (*P* < 0.05). Among all groups, nonallergic asthmatic patients with tinea (group 1) had the highest rate of positive skin tests to *T. rubrum*; however, this was not statistically higher than those for groups 2 and 4 (*P* > 0.05) (Table 2). The rate of positive skin tests for *T. rubrum* was 1.96 times higher in group 1 than group 2 without indicating a significant risk (rr:1.96, 95% CI:0.50–7.72) (*P* > 0.05).

Table 1. Groups and demographic characteristics of patients (average ± SD)

	<i>n</i>	F/M	Age (years) average ± SD
Group 1: nonallergic asthma (+) and dermatophyte infection (+)	19	12/7	42.2 ± 11.3
Group 2: allergic asthma (+) and dermatophyte infection (+)	15	7/8	37.3 ± 8.1
Group 3: asthma (+) dermatophyte infection (–)	22	16/6	36.3 ± 7.3
Group 4: dermatophyte infection (+) asthma (–)	17	9/8	42.6 ± 12.9
Group 5: healthy controls	13	11/2	29.8 ± 13.9
Total	86	55/31	38.6 ± 11.0

Table 2. Percentage of positive skin tests and specific IgE to *T. rubrum* in groups

	Patients <i>n</i>	Positive skin tests <i>n</i> (%)	IgE CAP class	
			<i>n</i> (≥ +2)	<i>n</i> (+1)
Group 1	19	12 (63.1)	3	1
Group 2	15	7 (46.7)	3	1
Group 3	22	*1 (4.5)	1	
Group 4	17	8 (47.05)	1	1
Group 5	13	*1 (7.7)		

* Groups 3 and 5 differed from other groups ($P > 0.05$).

In vitro tests

Serum specific IgE to *Trichophyton* was positive in a few cases with positive intradermal tests to this antigen. Specific IgE results are shown in Table 2.

Disease severity

When three groups of asthmatic patients (groups 1, 2, and 3) were evaluated according to disease severity, the rates of severe asthmatics were 31.6%, 13.3%, and 9.1% in groups 1, 2, and 3, respectively ($P > 0.05$). Among asthmatic patients with tinea, the rate of severe asthmatics was 23%, whereas severe asthmatics comprised 9% of the asthmatic patients without dermatophyte infection ($P > 0.05$). The rates of patients with the severe form of the disease were 30% and 13% in patients with positive and negative skin tests to *T. rubrum*, respectively ($P > 0.05$).

Mycologic findings

Fungal cultures were positive in 31 patients (60.8%) among 51 subjects with positive direct microscopy. Cultures revealed *T. rubrum* (58.1%), *T. mentagrophytes* (35.55), and *Candida* (6.4%) in these cases. Three groups did not differ in respect to the rate of positive cultures ($P > 0.05$) (Table 3). The skin test positivity rate to *T. rubrum* was not different between patients with positive cultures for either *T. rubrum* (10 out of 18) or *T. mentagrophytes* (5 out of 11) ($P > 0.05$).

Discussion

Although *Trichophyton* extracts are most commonly used to test for delayed-type hypersensitivity, it has been reported that about 5% of the general population may have positive immediate-hypersensitivity reactions to this antigen (2, 12–14). The possible role of *Trichophyton* allergy in asthma, rhinitis, and urticaria has been discussed since the 1930s. Ward et al. have described several patients with tinea in whom immediate hypersensitivity to dermatophyte antigens was present in association with perennial asthma, eosinophilia, and chronic rhinosinusitis (2). The specific sensitization of upper airways and bronchi was clearly

documented by nasal and bronchial provocation with *Trichophyton* extracts (2, 7). The present study aimed to determine the factors playing a role in *Trichophyton* sensitivity in patients with asthma, since most of the results in the literature are based on individual cases or small study groups focusing on the causal relationship of *Trichophyton* sensitization to intrinsic asthma, perennial rhinitis, and urticaria. In our study, subjects with tinea – whether asthmatic or not – had higher rates of *Trichophyton* sensitivity as determined by intra-dermal tests. However, in the absence of *Trichophyton* infection, the skin test positivity rate to *T. rubrum* was lower in both asthmatics and healthy controls. According to these results, the presence of fungal infection seems to be the crucial determinant of *Trichophyton* sensitivity. In a recent study, Escalaute et al. investigated the association of *Trichophyton* infection and atopy (15). They reported that having atopic disease did not cause a particular predisposition to chronic dermatosis, and that *Trichophyton* infection did not seem to be a frequent etiologic factor in atopic disease. Similarly, having asthma or an atopic state without dermatophyte infection did not seem to have an effect on *Trichophyton* sensitivity in our study population.

Although a large proportion of adult asthmatic patients are considered to have “intrinsic asthma”, there have been few studies on the specific pathogenesis of these cases. In this group of asthmatic patients, it has been suggested that *Trichophyton* should be considered a possible “intrinsic” allergen (2, 4). Furthermore, Ward et al. recently reported on patients with severe or moderately severe asthma with trichophytosis whose asthma improved after fluconazole treatment (6). Among the five groups in our study, the prevalence of *Trichophyton* sensitivity was highest in nonallergic asthmatics. Although the rate of severe asthma was 24.2% in all asthmatics, it was highest (31.6%) in the nonallergic group. It is clear that this is a relatively higher rate, as severe subjects comprised 7% of the adult asthmatic patients admitted to our outpatient clinic (unpublished data). Since immediate hypersensitivity to *Trichophyton* and the rate of severe asthma were higher – although not statistically significantly so – in

Table 3. Percentages of culture-positive subjects in various groups

	Direct (+) evaluation <i>n</i>	Culture (+) <i>n</i> (%)	<i>T. rubrum</i> <i>n</i>	<i>T. mentagrophytes</i> <i>n</i>	<i>Candida</i> <i>n</i>
Group 1	19	10 (52.6)	7	2	1
Group 2	15	9 (30)	4	4	1
Group 3	(–)	(–)	–	–	–
Group 4	17	12 (70.6)	7	5	–
Group 5	(–)	(–)	–	–	–
Total	51	31 (60.8)	18	11	2

* There was no difference between groups ($P > 0.05$).

nonallergic asthmatics in our study group, and there is convincing evidence that antifungal treatment causes a marked improvement in asthma symptoms, we may suggest that patients with nonallergic asthma should be examined for signs of fungal infection and tested for *Trichophyton* sensitivity.

In addition to skin test reactivity to *Trichophyton*, we also measured IgE antibody to this antigen. The measurement of IgE antibody to *Trichophyton* has been the subject of many studies. There have been reports on an ELISA technique for measuring IgE antibody to *Trichophyton* antigen (16). The other technique reported was crossed-radioimmuno-electrophoresis (CRIE), which is difficult and time-consuming, and yields only semiquantitative results (17). Recently, a RAST technique was developed for *T. tonsurans* extract by Platts-Mills et al., by which it has been possible to measure IgE antibody to *T. tonsurans* in most sera from skin-test-positive individuals (18). We used the UniCAP System, which is based on the fluoroenzyme immunoassay, and, surprisingly, among 29 skin test positive patients, eight had detectable IgE antibody to *Trichophyton*. Even with the inclusion of class I results in the evaluation, the number of patients with positive IgE antibody to *Trichophyton* did not reach higher levels. To our knowledge, there is no currently available report on positive UniCAP results; therefore, at present, it is difficult to discuss whether this method works with low specificity for *Trichophyton* antigens. However, considering the good correlation between patient skin test positivity and serum IgE levels to *Trichophyton*, as shown by RAST, we can speculate that the lack of similar findings in our patients may be related to the sensitivity of the method used in IgE measurement.

Fungi in the *Trichophyton* genus (*T. rubrum*, *T.*

mentagrophytes, and *T. tonsurans*) are known to colonize and infect keratinized human tissues. It is reported that almost all chronic dermatophyte infections of the skin involve *T. rubrum* (12). Fungal cultures of the feet and/or toenails were positive in 60.8% of subjects with positive direct microscopic evaluation in our study, the highest rate (58%) of positivity being to *T. rubrum*. When we evaluated the rate of positive skin tests to *T. rubrum* antigen among patients with positive cultures for different *Trichophyton* species, we found no difference in skin test positivity between the *T. rubrum* and *T. mentagrophytes* groups. This finding seems to indicate cross-reactivity between the species.

In conclusion, our results indicate that the presence of fungal infection was the main determinant in the development of *Trichophyton* sensitivity. Secondly, having asthma and/or an atopic state without dermatophyte infection did not seem to be associated with *Trichophyton* allergy. However, the rates of *Trichophyton* allergy and severe asthma were slightly higher in the group with nonallergic asthma. In view of these findings in the nonallergic and severely asthmatic groups in our study and the encouraging results of antifungal treatments in previous reports, we suggest that patients with severe, intrinsic asthma should be examined for signs of fungal infection, and if it is present, they should be tested for immediate hypersensitivity to *Trichophyton* antigens.

Acknowledgments

We thank Dr Platts-Mills for his valuable comments and critical review. This study was supported by a grant from the Scientific and Technical Research Council of Turkey (TUBITAK) – Health Sciences Research Committee – (SBAG-AYD-163).

References

1. WISE F, SULZBERGER MB. Urticaria and hay fever due to *Trichophyton*. JAMA 1930;**95**:1504–1508.
2. WARD GW, KARLSSON G, ROSE G, PLATTS-MILLS TAE. *Trichophyton* asthma: sensitisation of bronchi and upper airways to dermatophyte antigen. Lancet 1989;**8643**:859–862.
3. SCHWARTZ HJ, WARD GW. Onychomycosis, *Trichophyton* allergy and asthma – a causal relationship? Ann Allergy Asthma Immunol 1995;**74**:523–524.
4. PLATTS-MILLS TAE, CALL RS, DEUELL BA, KARLSSON G, WARD GW. The association of hypersensitivity diseases with dermatophyte infections. Clin Exp Allergy 1992;**22**:427–428.
5. PLATTS-MILLS TAE, FIOCCO GP, POLLART SM, HAYDEN ML, JACKSON S, WILKINS SR. *Trichophyton* allergy in a 24-year-old man with intrinsic asthma. Ann Allergy 1986;**56**:454–455, 470–471.
6. WARD GW, WOODFOLK JA, HAYDEN ML, JACKSON S, PLATTS-MILLS TAE. Treatment of late-onset asthma with fluconazole. J Allergy Clin Immunol 1999;**104**:541–546.
7. KIVITY S, SCHWARZ Y, FIREMAN E. The association of perennial rhinitis with *Trichophyton* infection. Clin Exp Allergy 1992;**22**:498–500.
8. WILSON BB, DEUELL B, PLATTS-MILLS TAE. Atopic dermatitis associated with dermatophyte infection and *Trichophyton* hypersensitivity. Cutis 1993;**51**:191–192.
9. GUMOWSKI P, LECH B, CHAVES I, GIRARD JP. Chronic asthma and rhinitis due to *Candida albicans*, *Epidermophyton*, and *Trichophyton*. Ann Allergy 1987;**59**:48–51.
10. DAVIES RR, GANDERTON MA, SAVAGE MA. Human nail dust and precipitating antibodies to *Trichophyton rubrum* in chiropodists. Clin Allergy 1983;**13**:309–315.
11. Guidelines for the diagnosis and management of asthma; highlights of the expert panel report 2. NIH Publication no. 97–4051A, 1997.
12. DAHL MV, GRANDO SA. Chronic dermatophytosis: what is special about *Trichophyton rubrum*? Adv Dermatol 1994;**9**:97–111.

13. DEUELL B, ARRUDA LK, HAYDEN ML, CHAPMAN MD, PLATTS-MILLS TAE. *Trichophyton tonsurans* allergen. I. Characterization of a protein that causes immediate but not delayed hypersensitivity. J Immunol 1991;**147**:96–101.
14. WOODFOLK JA, SLUNT JB, DEUELL B, HAYDEN ML, PLATTS-MILLS TAE. Definition of a *Trichophyton* protein associated with delayed hypersensitivity in humans. Evidence for immediate (IgE and IgG4) and delayed hypersensitivity to a single protein. J Immunol 1996;**156**:1695–1701.
15. ESCALANTE MT, SANCHES-BORGER M, CAPRILES-HULETT A, BELFORT E, DI BIAGIO E, GONZALES-AVELEDO L. *Trichophyton* specific IgE in patients with dermatophytosis is not associated with aeroallergen sensitivity. J Allergy Clin Immunol 2000;**105**:547–551.
16. HAY RJ, REID S, TALWAT E, MACNAMARA K. Immune responses of patients with tinea imbricata. Br J Dermatol 1983;**108**:581.
17. SVEJGAARD E, CHRISTIANSEN AH, STAHL D, THOMSEN K. Clinical and immunological studies in chronic dermatophytosis caused by *Trichophyton rubrum*. Acta Derm Venereol (Stockh) 1984;**64**:495.
18. PLATTS-MILLS TAE, FIOCCO GP, HAYDEN ML, GUERRANT JL, POLLART SM, WILKINS SR. Serum IgE antibodies to *Trichophyton* in patients with urticaria, angioedema, asthma, and rhinitis: development of a radioallergosorbent test. J Allergy Clin Immunol 1987;**79**:40–45.