

**TRICHOPHYTON ASTHMA: SENSITISATION
OF BRONCHI AND UPPER AIRWAYS TO
DERMATOPHYTE ANTIGEN**

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Summary 12 adult patients with perennial asthma and chronic skin infection were found to have immediate hypersensitivity to *Trichophyton* spp. 10 patients were tested by bronchial provocation and gave immediate bronchial reactions to an extract of *T tonsurans*. Double-blind, placebo-controlled nasal challenge of 8 patients demonstrated that the upper airways of these patients were also sensitive to this dermatophyte antigen. In addition to perennial asthma most of the patients had persistent eosinophilia and chronic rhinosinusitis. The results suggest that absorption of fungal antigen can give rise to IgE antibody production, sensitisation of the airways, and symptomatic asthma and rhinosinusitis. Several patients had many of the features of late onset or "intrinsic" asthma.

Introduction

THE observation by Charles Blackley¹ 100 years ago that inhaled fungi could induce asthma has been repeatedly confirmed. These airway responses correlate with positive immediate skin tests and the presence of serum IgE antibodies.² In 1930 Wise and Sulzberger³ described a patient with asthma and severe tinea infections, whose asthma improved with treatment of the fungal infection. When this patient was tested intradermally with trichophyton extract she had itching, urticaria, violent sneezing, and dyspnoea. There have been subsequent reports of dermatophyte sensitivity associated with either asthma or urticaria.⁴⁻⁸ Also chiropodists may have immune responses to and symptoms from trichophyton exposure,

presumably after inhalation of antigens while grinding infected toenails.⁹ Immediate hypersensitivity to dermatophyte antigens may be common in patients with more severe fungal infections, which has been attributed to failure of protective delayed hypersensitivity.¹⁰⁻¹² Jones et al¹³ reported cross-sensitivity between trichophyton and a range of inhaled fungi, casting doubt on the specificity of the responses to trichophyton.¹³

We have reported that serum IgE antibody levels to trichophyton correlated well with immediate skin-test reactions in adults with urticaria, angio-oedema, rhinitis, or asthma.⁸ We found little evidence for cross-reactivity with other fungi or antigens. We also reported a trichophyton-sensitive patient whose asthma improved, and remains controllable, after the start of local treatment of dermatophyte infection.¹⁴ We now report 12 patients with asthma, dermatophyte infection, and immediate hypersensitivity to trichophyton. Our aim was to investigate whether these patients have trichophyton-specific sensitisation of their upper airways and bronchi.

Patients and Methods

Patients

We studied 12 adult male patients who had a documented history of reversible airway obstruction and an 8 × 8 mm wheal 15 min after an intradermal test with mixed trichophyton extract (2 × 10⁻² w/v or less; Hollister-Stier, Spokane, Washington). 15 adult volunteers (9 male), who included 5 asthmatic patients, gave negative immediate skin responses to trichophyton, and had no detectable (ie, less than 7 units) IgE antibody to trichophyton, served as controls. 10 of the group of 12 patients were studied with bronchial provocation. Written consent was obtained from all subjects and every procedure was approved by the University of Virginia human investigation committee.

Extracts and Skin Testing

T tonsurans dried mat was provided by Hollister-Stier and extracted for 12 h in physiological saline (10⁻¹) and dialysed against two changes of saline for 24 h. The extract was freeze-dried in 5 ml amounts and reconstituted and filtered before use. Skin titration with *T tonsurans* extract was done on the volar surface of the arm

with a 26 G needle, starting at 10^{-5} w/v in 30 μ l. Immediate reactions were read at 15 min with an end-point of an 8×8 mm or larger wheal. Late and delayed reactions were recorded by the patients in mm of induration at 6, 18, 24, 48, and 72 h.

Bronchial Provocation

Bronchial challenges were done by the 2 min tidal volume method with a De Vilbiss pump and Air Life (American Pharmaceutical Co) nebuliser containing 2.5 ml solution.¹⁵ Where possible adrenergic agents, oral and inhaled, and theophylline preparations were withheld for 12 h before provocation testing. Antihistamine and sodium chromoglycate preparations were withheld for 48 h. No patients were receiving hydroxyzine or anticholinergic drugs. In 2 cases inhaled β_2 -agonists were withheld for only 6 h before testing because of symptoms, and 1 patient was not tested because his forced expiratory volume in 1 s (FEV₁) never reached 50% of predicted. For histamine provocation tests, histamine acid phosphate was diluted from a stock solution of 16 mg/ml, passed through an 0.22 μ m filter, and prepared in doubling dilutions from 2 to 0.0625 mg/ml. A FEV₁ drop of 20% or more from baseline with 1 mg/ml histamine or less was regarded as positive. Antigen solutions of trichophyton, cat dander, *Dermatophagoides farinae*, and rye grass pollen were dialysed, filtered, and diluted in saline. *T. tonsurans* was administered in increasing half-log concentrations starting at 10^{-4} w/v or less depending on skin sensitivity. A fall of 20% in FEV₁ was regarded as positive, and patients who had symptoms 15 min after a positive bronchial challenge were treated with nebulised salbutamol. 4 patients were admitted to our clinical research centre for observation; however, none had late reactions requiring further treatment. Subjects were given a Wright peak-flow meter to record peak expiratory flow at 6, 18, 24, 48, and 72 h after bronchial challenge.

Nasal Provocation

Nasal challenge was done as a double-blind, placebo-controlled crossover study. Before challenge all patients underwent anterior rhinoscopy and there were no major pathological findings (tumours, polyps, or septal deviation). The patients were randomly allocated to start nasal challenge with either placebo or *T. tonsurans* extract. Solutions were prepared on the same day as the challenge, which was done with two 0.26 ml sprays in each nasal cavity starting with 10^{-5} w/v and increasing up to 10^{-2} . 15 min were allowed between each challenge and at least 2 h between challenge with

placebo and active solutions. Nasal peak expiratory flow was recorded before and after every step. The number of sneezes was counted and the degree of congestion and secretion was estimated by the patients on a scale from 0 to 4 (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = intolerable). The number of sneezes was scaled to zero sneezes = 0, 1-3 = 1, 4-6 = 2, 7-9 = 3, and 10 or more = 4. The scores for congestion, secretion, and sneezing at every step were summed (maximum 12).

Radioallergosorbent Test

Serum IgE antibodies to trichophyton were measured by radioallergosorbent test, with *T. tonsurans* extract linked to 'Sepharose 4B' (Pharmacia). Units for IgE antibodies were obtained from a control curve.⁸

Results

The clinical features, skin test results, and the levels of serum IgE antibodies to *T. tonsurans* are shown in table 1. All the patients had signs of fungal infection on their skin or toenails and all had asthma, which was severe in 4 cases (ie, on oral steroids for more than a year). In addition, 8 patients had required treatment for rhinitis, including operations in 5 cases, and 7 had evidence of chronic rhinosinusitis on X-ray. In 5 patients asthma started before the age of 10 years and these patients had multiple positive skin tests. In contrast asthma started in 3 patients over the age of 20 years, and these 3 had no other positive skin tests, except for that to *T. tonsurans*.

Bronchial Provocation

Fourteen of fifteen *T. tonsurans* bronchial challenges in 10 patients were positive (table II). The one negative challenge was observed in patient 2 after two positive challenges several months earlier. 15 controls gave negative challenges with 1:10 extract of *T. tonsurans*, and the difference in the maximum observed fall in FEV₁ was significant (unpaired t test, $p < 0.001$) (fig 1). 4 of the trichophyton positive patients gave no response when challenged with other antigens to which they were skin test negative. In addition, 4 of the negative controls were asthmatic and gave positive bronchial responses to an antigen to which they had a positive skin test (data not shown).

TABLE 1—CLINICAL DETAILS OF 12 MEN WITH ASTHMA, SIGNS OF FUNGAL INFECTION, AND POSITIVE SKIN TESTS TO TRICHOPHYTON

Patient (age [yr])	Asthma		Other positive skin tests	<i>T. tonsurans</i> IgE anti- body titre	Eosinophils (%)†	Chronic rhino- sinusitis‡	Fungal infection		
	Age at onset (yr)	Severity*					Site	Treatment§	Response*
1 (52)	<10	Moderate	Fungi	55	6	—	Feet	Clotrimazole	++
2 (24)	22	Severe	...	23	13	—	Skin	Clotrimazole	++
3 (56)	53	Moderate	Fungi	22	11	—	Skin	Clotrimazole	±
4 (23)	<10	Mild	Cat, mite	229	7	—	Feet	Clotrimazole	++
5 (36)	<10	Mild	Cat, mite	100	4	—	Feet	Clotrimazole	+
6 (44)	<10	Moderate	Cat, fungi	187	20	—	Feet	Clotrimazole	+
7 (45)	44	Severe	...	62	8	—	Feet	...	...
8 (69)	60	Mild	...	13	13	—	Nails	Griseofulvin	+
9 (57)	53	Severe	Mite	1076	6	—	Nails	Griseofulvin	++
10 (50)	47	Moderate	Mite, fungi, grasses	67	8	—	Nails	Griseofulvin	±
11 (50)	39	Severe	Grass, fungi	350	2	—	Feet	Clotrimazole	+
12 (53)	<10	Moderate	Mites	14	15	—	Feet, groin	Griseofulvin	—
							Feet	Griseofulvin	++

*Severe = on oral steroids for over a year; moderate = recurrent acute attacks requiring steroid courses as well as chronic theophylline and bronchodilator therapy; mild = chronic symptoms requiring bronchodilator therapy and theophylline or inhaled steroids or sodium chromoglycate.

†Patients 1, 7, 9, and 11 were on oral steroids at time of testing.

‡Chronic rhinosinusitis was judged on basis of symptoms plus objective findings on sinus X-ray. Patients 2, 3, 8, 11, and 12 had had nasal sinus operations and had polyp formation.

§Clotrimazole as ointment; griseofulvin given orally, combined with clotrimazole ointment.

*Response = subjective assessment of improvement in asthma symptoms since start of antifungal therapy.

TABLE II—BRONCHIAL PROVOCATION WITH TRICHOPHYTON

Patient*	Skin test (w/v)†	Bronchial challenge			
		Baseline FEV ₁ (l)	Maximum fall (%)	Dose w/v	Late phase‡
1§	10 ⁻³	a) 2.92	21	10 ⁻¹	±
		b) 2.49	41	2 × 10 ⁻²	++
2§	10 ⁻⁴	a) 2.12	24	10 ⁻²	—
		b) 2.16	23	10 ⁻³	++
		c) 2.4	3	...	+
3	2 × 10 ⁻³	2.8	32	2 × 10 ⁻³	+
4	10 ⁻⁶	a) 6.44	51	10 ⁻²	±
		b) 6.37	56	10 ⁻²	±
5§	10 ⁻⁴	3.11	56	10 ⁻²	++
6§	10 ⁻³	2.96	40	10 ⁻³	—
7§	2 × 10 ⁻⁴	a) 1.84	21	10 ⁻¹	++
		b) 1.69	21	10 ⁻¹	++
10§	10 ⁻⁵	3.31	44	10 ⁻¹	±
11	10 ⁻²	2.34	30	10 ⁻⁴	++
12	2 × 10 ⁻³	1.39	30	10 ⁻²	++

*2 patients did not have bronchial provocation: patient 8 has never had FEV₁ over 50% of predicted and patient 9 was unavailable.

†8 × 8 mm wheal 15 min after intradermal testing.

‡Late phase responses were assessed by repeated peak flow measurements over 72 h: ++, >15% reduction; +, >10%; and ±, 5–10% reduction.

§Positive histamine provocation: ≥20% fall in FEV₁ to 1 mg/ml or more histamine.

Nasal Provocation

When tested by double-blind nasal challenge, 7 of 8 patients gave a positive reaction in one or more of the four values recorded. The patient without any nasal symptoms after challenge (patient 9) had a bronchial reaction with a 40% fall in FEV₁ after nasal challenge with 10⁻³ trichophyton extract, which precluded further nasal provocation. The following significant differences were found between placebo and active nasal challenge with 10⁻² extract (paired t test): nasal peak expiratory flow ($p < 0.01$), sneezes ($p < 0.01$), secretion ($p < 0.01$), and congestion ($p < 0.05$). The difference in total nasal score between placebo and trichophyton 10⁻² extract challenges was also significant (fig 2).

Delayed and Late Responses

Studies on late bronchial reactions were restricted because 8 of the 10 patients who were challenged required

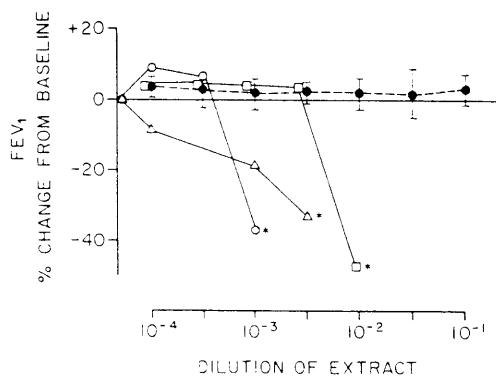
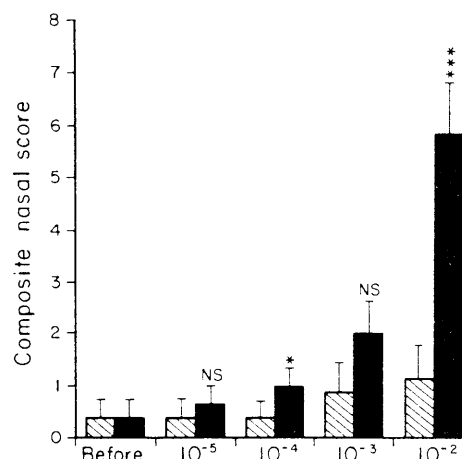


Fig 1—Bronchial provocation with trichophyton extract.

Results are shown for trichophyton sensitive asthmatic patients (no 3, 4, and 6; open symbols) and for 15 controls (mean [SD] closed circles). Patients were treated with salbutamol* to reverse bronchospasm.



Trichophyton extract concentration (w/v)

Fig 2—Double-blind nasal challenge with trichophyton in 8 patients.

Patients were challenged with serial dilutions of trichophyton (solid bars) or placebo (hatched bars). Significant difference between corresponding placebo step and active challenge: * $p < 0.05$ and *** $p < 0.001$.

regular treatment for asthma. However, seven of the positive provocations were followed by a persistent fall in peak expiratory flow for 28–48 h. Only 1 out of 14 controls responded similarly. Delayed skin responses to trichophyton are common in adults, and 9 of 11 controls showed 8 × 8 mm of induration and erythema at 24 h. In 3 controls induration and erythema were 10 × 10 mm by 6 h. Only 2 of 9 patients showed 8 × 8 mm induration at 24 h and 7 of the patients showed no detectable (ie, less than 2 × 2 mm) skin reaction at 24 or 48 h. These results confirm that a positive immediate skin reaction to trichophyton is often associated with an absent delayed reaction.^{10–12,16} There was no relation between delayed skin responses and delayed or late bronchial responses to trichophyton.

Discussion

Trichophyton infection of the skin or toenails is common and in many adults delayed hypersensitivity to this antigen develops. Indeed trichophyton is routinely used in a panel for testing for delayed hypersensitivity or for producing T-cell proliferation in vitro. Immediate hypersensitivity to trichophyton develops in about 5% of individuals and the association with urticaria, asthma, and rhinitis has been observed among this group.⁸ The development of T-cell sensitisation is widely assumed to be secondary to absorption of antigen through the often ulcerated skin, and the production of IgE antibody is probably induced by the same route. Furthermore the association with urticaria strongly suggests systemic absorption since the inhalation of antigens is an unusual cause of urticaria.^{4,5,7,8} Because of the unusual route of sensitisation and the doubts about the specificity of hypersensitivity to trichophyton we felt it essential to establish that the airways of our patients were indeed sensitive to trichophyton. Specificity of these responses was supported by the lack of response in patients who were skin test negative, including asthmatic cases, the absence of response of these patients to several other antigens, and, in 6 cases, the absence of skin responses to any of a panel of sixteen fungi which commonly give rise to

sensitisation. Recent work in our laboratory has further supported this view by showing for three sera that less than 10% of the IgE antibody to trichophyton could be absorbed with either alternaria or aspergillus immunosorbent (B. Deuell, M. D. Chapman, and T. A. E. P-M, unpublished). We now feel it unlikely that the IgE antibody to trichophyton found in the serum of these patients can be explained by cross-reactivity with other fungi.

Only a small proportion of patients with asthma have immediate skin sensitivity to trichophyton. Of 102 adults treated in a hospital emergency room 66 (65%) had IgE antibody to at least one common inhalant antigen and only 2 had detectable serum IgE antibody to trichophyton.¹⁷ Among asthmatic adults referred to the University of Virginia outpatient clinics, trichophyton skin tests are positive in about 10% of patients. Rackemann¹⁸ drew attention to a group of patients with late onset, usually severe, asthma, often associated with nasal polyposis and eosinophilia.¹⁸ 4 of our patients (no 2, 3, 7, and 8) would in most clinics fit the criteria for "intrinsic" asthma. Our results raise the question whether other fungi growing on skin or mucosal surfaces (eg, *Aspergillus* or *Candida* spp) can give rise to similar sensitisation and disease.^{19,20} In allergic bronchopulmonary aspergillosis it is assumed that fungus growing in the lung sensitises and inflames the lung by local exposure. However, in this condition, the fungus can usually be grown from sputum.²¹ The relevance of our observations to the management of asthma depends on whether treatment of the fungal disease will help the asthma. Our experience has been encouraging in that we have now seen 8 patients where antifungal treatment has produced an improvement in symptoms with reduced requirement for treatment and/or improved function. The question whether antifungal drugs should be used in these patients is made more interesting by the recent introduction of more effective azole compounds.^{22,23}

8 of our patients had a history of persistent nasal symptoms and 5 of them had had chronic rhinosinusitis requiring nasal surgery. In 6 cases the nasal symptoms preceded asthma by 1 to 10 or more years. The double-blind nasal challenge showed that their noses were sensitised to trichophyton. These observations suggest that trichophyton sensitivity can give rise to chronic sinusitis with or without polyps. Again we assume that the antigen is absorbed. However, two other routes of exposure are possible: the antigen could be inhaled from floor dust, as reported for chiropodists, or the antigen could be present in the nose. All the patients who were challenged nasally were also cultured for fungi and their secretions were examined microscopically for hyphae: no evidence was obtained for local growth of trichophyton in the nose, and no abnormal mucosal lesions were observed.

A striking feature of our patients and of intrinsic asthma is the presence of persistent eosinophilia.¹⁸ Current understanding of eosinophil production from the bone marrow suggests that the most likely mechanism is production of eosinophil differentiation factor (interleukin-5) by T cells.²⁴ Most patients with immediate hypersensitivity to trichophyton have little or no delayed skin response, and it seems likely that the T-cell response to trichophyton in patients who make IgE antibodies is different from that in most patients who have delayed hypersensitivity only.²⁵ Thus the nature of the T-cell response may influence both the isotype of the antibody response and the presence or absence of eosinophilia.

Individuals who acquire immunity to trichophyton antigens generally make either a delayed hypersensitivity response or an IgE antibody response. Rhinosinusitis and/or asthma develops in some individuals who have immediate hypersensitivity to trichophyton, and these patients' airways are specifically sensitised to trichophyton. Our results suggest that adults with perennial asthma should be examined for signs of fungal infection and tested to evaluate immediate hypersensitivity to dermatophyte antigens. Furthermore our clinical experience suggests that specific antifungal treatment is both safe and beneficial in this group of patients.

This study was supported by NIH grant AI20565 and RRO 0847 General Clinical Research Center. G. K. is the recipient of grants from the Swedish Medical Research Council (K88-17F-8419-01), the Swedish Medical Association, and the Swedish Society of Medicine.

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