

TRICHOPHYTON ALLERGY: REVIEW OF 89 CASES

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SUMMARY: A series of 89 cases (55 men 34 women) of Trichophyton allergy is presented. All the patients had a clinical history and in 86 out of 89 lesions of dermatophytosis urticaria/angioedema was present in 57, eczema in 8, rhinitis in 12, conjunctivitis in 1 and asthma in 12. Skin prick tests to Trichophyton were positive in 53 (59,6%) of the patients and intradermal test in all. Specific IgE was found in 45 (69,3%) out of 70 patients. Antifungal treatment was effective at mean term in 18 cases. Specific immunotherapy was evaluated in 54 with good or very good results in 41 (83,3%). Trichophyton dermatophytosis must be looked for in all the cases of urticaria/angioedema and most cases of respiratory allergy without clear allergy to inhalants.

Key-words: Trichophyton - Allergy - Dermatomycosis - Specific Immunotherapy.

Allergic diseases due to Trichophyton species were currently quoted in medical literature 20 to 30 years ago (Aas, Blamoutier, Hay, Hanifin, Kudelko, Sayag, Schlafer, Thiers). However in the last few years fungal allergy was almost been banned from medical literature and the importance of Trichophyton in some cases of allergy is denied (Gern, Kaplan, Panzani, Turup). Allergenic extracts obtained from Trichophyton species are scarcely available and standardized extracts very difficult to obtain. As long as we know for the time being only Allergopharma-Merck Germany and Lofarma Italy are still producing Trichophyton extracts either for diagnostic purposes or for eventual immunotherapy. Research specific IgE for diagnosis is only available from Phadia and only for Trichophyton rubrum while the reactives for Trichophyton mentagrophytes and Trichophyton interdigitale are only available for research purposes.

Skin tests with Trichophyton extracts are seldom used in clinical daily practice except by some Allergy groups including specialists with some decades experience. In general a systematic sequence of prick skin tests and intradermal tests with different Trichophyton extracts and major Trichophyton species, rubrum, verrucosum, interdigitale, tonsurans and mentagrophytes are not included in standard diagnostic procedures for allergy diagnosis. However among adult patients with respiratory allergy or urticaria there is a significant number who have over fun-

gal infection of their feet, toenails and/or groin (Platts-Mills 1992). Even if skin prick tests in these patients are seldom positive to Trichophyton extracts in a few cases there is a clear-cut positive results in prick. Intradermal skin testing always confirm in general these results. Positive wheal and flare reactions to intradermal tests with Trichophyton extracts using 0,02 ml of a 1/100 or 1/1000 dilution are not uncommon in allergic patients with rhinitis, asthma or urticaria/angioedema. As quoted by Platts-Mill (31) some of these patients are only positive to Trichophyton or simultaneously positive to Trichophyton and Candida. In contrast with cases of Candida allergy which are much more frequent in women, Trichophyton allergy is more common in men. Present clinical data confirm the initial reports from WISE and Sulzberger (44) published in Jama in 1930 and the description of European authors mainly french 20 and 30 years ago, (Schlafer, Sayag, Aas, Blamoutier, Thiers).

Immediate reactions to Trichophyton have been reported by many authors (Lehman, Macotella-Ruiz, Calderon, Wood, Jones, Hanifin, Hay). These immediate reactions in most cases due to IgE are more common in chronic infections mainly interdigital mycosis or onychomycosis (Lehman, Jones, Hanifin).

The proteins implied in these immediate reactions have been characterized by Deuell, Arruda and al. in 1991. This protein is different of the proteins responsible by delayed hypersensitivity in Trichophyton infections. However some patients appear to give a wheal reaction prior to a delayed hypersensitivity response

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and this wheal and flare does not correlate with IgE. This result is very important as quoted by *PLATTS-MILLS* in 1992 because it means that wheal and flare response are not necessarily IgE mediated (*Platts-Mills 1992*) the implication of basophils in immediate and late hypersensitivity reactions to *Trichophyton* are not completely clarified (*Askenase 1979*).

Some cases of urticaria at least associated with *Trichophyton* infections are nowadays considered as the modern mood as auto-immune urticaria even if self test is negative and of asthma or rhinosinusitis as intrinsic.

In 1987 the group from Genève led by *J.-P. Girard* reported chronic asthma and rhinitis due to *Candida albicans*, *Epidermophyton* and *Trichophyton* (*Gumowski, Lech et al. 1987*) and in 1989 and 1982 *Platts-Mills* group describes 11 cases of asthma due to *Trichophyton* confirming an anterior report (*Platts-Mills 1986*). This same year *Platts-Mills, Fiocco et al.* developed a radioallergosorbent test to *Trichophyton* (*Platts-Mills 1987*) and in the nineties the same authors started the use of antifungal drugs in chronic fungal infection in asthmatic patients as an adjunct treatment.

Some reports of successful immunotherapy in *Trichophyton* linked allergy have been published many years ago (*Beemer 1977, Jones 1979*) as well as successful immunotherapy for other fungal infections (*Moraes 2000, Palma-Carlos 2004*).

Many reports of association of *Trichophyton* infections with chronic urticaria have been published (*Jones, May, Hanifin, Schlafer, Thiers, Palma-Carlos, Kamma et al. 2006*) and many patients responded well to antifungal treatment (*Fiocco, Wilkins et al. 1986, Palma-Carlos, Kamma et al. 2006*). However there are few published studies of immunotherapy with *Candida albicans* and *Trichophyton* and the characterization of these vaccines is usually poor (*Who 1998*).

In the present paper we will review a series of 89 cases of allergic patients with suspected *Trichophyton* allergy, confirmed in all the patients. The clinical aspects of allergy and dermatophytosis will be quoted as well as the results of skin tests in prick and intradermal, the research of specific IgE when available and the modalities of treatment including specific immunotherapy when considered and indicated. Results of therapy will be presented.

This series being collected in out-patients in a private Allergy Center has some limitations due to practical problems; non compliance of patients and the large period of selection (10 years) must be considered.

MATERIAL AND METHODS

The files of all patients seen in the last 10 years in the Clinical Allergy Immunology Center have been reviewed. The diagnosis of *Trichophyton* associated disease has been based on a clinical history of a cutaneous mycosis of the Dermatophytosis group either *tinea corporis*, *tinea inguinalis* or *cruris*, *tinea pedis* (athletes foot), *tinea manuum* or *onychomycosis* and on the objective examination confirming one of these Dermatophytosis and in some cases the protacted association of scrotal and perianal Candidiasis. Confirmations by research of fungi in cutaneous lesions has been done only in a limited number of patients.

Skin tests have been done first by prick with extracts from Allergopharma (Merck, Germany), Stallergenes (France) and in a second phase by intradermal method with 3 different extracts of *Trichophyton* species, *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Trichophyton interdigitale*. In all the patients skin tests for common inhalants, mites, pollens have also been done. Skin tests for food have been done when there was a suspicion of food allergy. Skin tests by prick and intradermal technique for *Candida albicans* have been done in all the patients. Intradermal skin tests for *Trichophyton* species as well as for *Candida* have always been read at 15-20 min. for immediate reactions, 6 hours for late reactions and 48 hours for delayed reactions. Clearly positive immediate reactions (equal or superior to histamine) only either in prick or intradermal have been considered as a proof of *Trichophyton* allergy.

Research of specific IgE antibodies for *Trichophyton rubrum* by UNICAP system (Pharmacia-Phadia) have been done in 70 cases. In the same cases specific IgE for *Candida* have also been searched.

Anti-fungal initial treatment has been tried in most cases when there was no medical contra indication for chronic hepatic disease or the risk of drug interactions, namely with macrolide antibiotics or first generation anti-histamines.

Specific immunotherapy with *Trichophyton* extracts from Stallergenes of Allergopharma has been tried at least initially in 71 patients by intradermal route in all the cases. Repeated evaluations of prick and intradermal skin tests and of specific IgE has been done after specific immunotherapy in some patients. Clinical results of specific immunotherapy have been evaluated at least all 2 and 3 years after starting.

RESULTS

From 9087 patients consulting in the Clinical Allergy tests in Lisbon in the last 10 years 89 (9,8%) has a clinical history and data of objective examination suggesting a Dermatophytosis 55 (61,8%) were male and only 34 (38,2%) female with a reverse pattern in relation to Candidiasis and Candida allergy, much more frequent in women (Palma-Carlos 2002, 2004).

From these 89 patients 61 (68,5%) had tinea pedis, 31 (34,9%) onychomycosis, 25 (28,1%) tinea cruris and 3 (3,4%) only pruritus without clear lesions but a clinical history of previous Dermatophytosis on a total of 120 dermatophytotic lesions. 31 of the patients (34,8%) presented more than a mycotic infection (table 1).

Allergic manifestations were present in all the cases (table 2): Urticaria and/or angioedema in 57 (63,6%), eczema in 8 (9,0%) rhinitis in 12 (13,5%), conjunctivitis alone in one patient (1,1%) and finally bronchial asthma always associated with rhinitis in 11 (12,4%).

Research of Tricophyton in skin lesions has been done only in 20 cases and was positive in 16 (80%) of these patients.

Prick skin tests to Tricophyton were positive in 53 (59,6%) of the patients and negative in the remaining 36 (40,4%) (table 3) but intradermal tests were clearly positive in all the 89 patients. Specific IgE

for Tricophyton rubrum was positive in 45 (69,3%) of the 70 patients where it has been studied and negative in the remaining 25 (35,7%). Range of positivity goes from more than 100 KUA/l 57,8% KUA/l, to 0,7 KUA/l, the majority of the cases being in classes 2 or 3 from 1,0 to 4,0 KUA/l. Comparing specific IgE with prick skin tests a concordance has been found in 56 (80,0%) of the patients and a discordance in 14 (20%). For intradermal tests specific IgE was concordant in 45 (64,3%) and discordant in 25 (35,7%) (table 4).

Antifungal treatment has cleared or much improved allergic manifestations in 18 (20,2%) of the patients. In the remaining 71 specific immunotherapy has been considered indicated.

Results of specific immunotherapy were available in 54 (76,1%) out of 71 patients where it has been tried. In the other 17, drop-out patient results were not evaluated due to non-compliance, rapid improvement or non attending the evaluation appointments (23,9%). 54 Patients were evaluated after specific immunotherapy: In 21 (38,9 %) urticaria or other allergic symptoms were completely cleared, in 24 (44,4%) a great improvement only occasional symptoms allergy was observed, in 3 (5,6%) a slight significant decrease in the number and intensity was obtained and in 6 (11,1%) there was no improvement. All together very good and good results were obtained in 55 (83,3%) of the patients treated by specific immunotherapy (Table V). A marked decrease

89 cases	
- Males 55 (61,8%) Females 34 (38,2%)	
DERMATOPHYTOSIS	
- Tinea Pedis	61 (68,5%)
- Onychomycosis	31 (34,8%)
- Tinea Cruris	25 (28,1%)
- Pruritus	3 (3,4%)

Table 1: Allergy to tricophyton

Allergic diseases	
- Urticaria/Angioedema	57 (64,0%)
- Eczema	8 (9,0%)
- Rhinitis	12 (13,5%)
- Conjunctivitis	1 (1,1%)
- Asthma	11 (12,4%)

Table 2: Allergy to tricophyton

Skin Tests		
	Positive	Negative
Prick Tests	53 (59,6%)	36 (40,4%)
Intradermal	89 (100,0%)	0 (0,0%)

Table 3: Allergy to tricophyton

Skin Tests and Specific IgE		
	Positive	Negative
Prick Tests		
Positive	38	7
Specific IgE		
Negative	7	18
Intradermal Tests		
Positive	45	0
Specific IgE		
Negative	25	0

Table 4: Allergy to tricophyton

Specific Immunotherapy 54 Patients Specific Immunotherapy Results		
Very Good	21 (38,9%)	83,3%
Good	24 (44,4%)	
Slight	3 (5,6%)	
Negative	6 (11,1%)	

Table 5: Allergy to tricophyton

of specific IgE was parallel to clinical improvement in a patient sequentially evaluated (PALMA-CARLOS, KAMMA *et al.* 2006).

DISCUSSION

A large series of Tricophyton allergy were scarcely or not at all reported in literature in the last decades or currently (AAS, DEUEL, DEZFOULIAN, HAWRA-NEK, PLATTS-MILLS, GUMOWSKI, HANIFIN, KURUP, SAYAG, SCLAFFER, WEARY, WISE). Short series have been published by PLATTS-MILLS group in the eighties and nineties and recently a report from a little bit larger series of 17 cases was presented by a brazilian group (OLIVEIRA, *et al.* 2006). In the present paper we have collected a very large group of patients with allergic diseases, namely urticaria-angioedema rhinitis and asthma related to Tricophyton allergy.

The large group of patients allows to define the Dermatophytosis lesions which can be the cause of allergic diseases and the most current clinical presentation of Tricophyton related allergy. More current mycotic lesions are in our series Tinea pedis, onychomycosis and tinea cruris which can be considered by most patients, and even by medical doctors as a banal ailment not easily cleared and not as a potential cause of allergy. The predominance of males in all the series including the present one is constant (PLATTS-MILLS *et al.* 1992, OLIVEIRA *et al.*). One possible explanation is due to a more active physical activity by men, including sports, pools etc. or careless feet by hygiene by the same group. As long as clinical allergy presentation urticaria/angioedema is the more frequent presentation but eczema, asthma and rhinitis can also be related to Tricophyton allergy. In contrast in the brazilian series from ARRUDA group (Oliveira *et al.*) asthma was more frequent - 11 out of 17 cases than urticaria/angioedema (5 out of 17).

Skin tests are a valuable tool for the diagnosis of Tricophyton allergy. However skin prick tests are not sufficiently sensitive in most cases when done with the currently available extracts to allow to confirm the diagnosis and intradermal tests have to be systematically done in a second time. False positive results cannot be excluded in some cases but in practice intradermal tests are more reliable than prick to point out to a Tricophyton allergy.

Specific IgE is only currently available for Tricophyton rubrum not for other species and the variations of antigenic mosaic between different Tricophyton species can explain the discordance in

some cases between skin prick tests, intradermal test and specific IgE. The sensitivity of specific IgE is in the present series is the same that for skin prick tests. Both skin and intradermal tests and the research of specific IgE have to be combined in order to increase the sensitivity of Tricophyton allergy diagnosis (Dezfoulan, De La Brassine).

A first line trial of antifungal therapy must be done in all patients unless there are medical contraindication (hepatic disease). The interactions of the conazole antifungal drugs with macrolide antibiotics and most anti-histamine have to be evaluated. The newer anti-histamine desloratadine and levocetirizine seems to be safer as long as interaction with conazoles is concerned.

Specific immunotherapy has been assayed mainly in cases of urticaria, but also in some cases of rhinitis. Overall results of specific immunotherapy were, in this open trial, very positive with a total 88,3% of good and very good results. Only local side effects have been reported without any severe reactions but the increase in the schedule must be carefully controlled by experimented allergists. A clear-cut decrease of specific IgE is parallel to the clinical improvement as shown in one patient (Palma-Carlos, Kamma *et al.* 2006) presenting a shift from more than 100 KUA/L for 0,7 KUA/L.

This large group of patients collected in our Clinical Allergy Center shows that Tricophyton allergy is not negligible, confirming the previous reports of Suzberger seventy years ago, Sclaffer thirty years ago and more recently Platts-Mills group (8, 31, 32, 33) and Arruda group (24).

Probably different mechanisms can be the cause of allergic reactions to Tricophyton, IgE antibodies, IgG antibodies and circulating immune complexes and cellular mechanisms. The results published confirm that specific IgE to Tricophyton allergens may be in cause in the pathogenesis urticaria/angioedema, rhinitis and asthma. The modern trend to consider most cases of urticaria as auto-immune (IG) has to be balanced in the search for other causes. Ignoring the data of basic clinical observation looking for Dermatophytotic lesions can lead to misdiagnosis in a large serie of allergic patients otherwise considered as intrinsic.

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