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Clinical and Immunological Studies in Chronic Dermatophytosis Caused by *Trichophyton rubrum*

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Twenty-six patients with chronic dermatophytosis (CD) by Trichophyton rubrum (TR) through one year were included in a double-blind clinical trial with Levamisole/Placebo. All patients were treated with griseofulvin concomitantly. Before, during and after the trial, studies of the cellular and humoral immune reponse were performed. The result of treatment with griseofulvin plus levamisole (62.5% cured or improved) did not differ from that of griseofulvin plus placebo (58% improved). All patients but one showed normal general cellular immune responses. Stimulation of lymphocytes with a specific TR antigen extract showed a significantly stronger response in the patient group than in the group of 39 controls ($p=0.01$–0.00003) at all investigation dates. Immediate weal reactions to the TR extract were seen in 42% of the patients and increased concentration of IgE antibodies was demonstrated in 46%. Specific IgG antibodies towards TR were observed in 42% of the patients. The presence of specific IgG antibodies and a strong specific cellular immune response were related to the severity of clinical involvement. Environmental factors and atopy were associated disorders in 81% and 77% respectively. *Key words: Levamisole; Cellmediated immunity; Humoral antibody response; Lymphocyte transformation in vitro; Intradermal test; Crossed immunoelectrophoresis.* (Received December 12, 1983.)

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By now, Trichophyton rubrum (TR) is the most frequently cultured dermatophyte in the mycological laboratories and is often responsible of multifocal and chronic usually mildly inflammatory infections of hands, feet, nails, groins or generalization. Severe itch or burning, painful fissuring and considerable hyperkeratosis of skin and nails may evolve. Topical or systemical treatment can lead to temporary improvement but rarely healing. This special host/parasite relationship constitutes a challenge for investigations of the possible causes of this condition, including studies of the antigenic and other biological properties of the fungus on one hand and the immune response of the host on the other. Impairment of the immune response due to immunosuppression with azathioprine and/or systemic treatment with steroids often provokes a formerly silent TR infection. Atopic patients, in whom immunological disorders might be present, are more susceptible to chronic TR infections (1, 2, 3). These observations led to the suggestion that chronic dermatophytosis (CD) caused by TR may be related to a general or specific immune deficiency. In the present study, a group of patients with CD was followed with clinical, mycological and immunological investigations through one year and a double blind clinical trial with Levamisole was included. This drug has been shown to restore the function of hypofunctional T lymphocytes and phagocytes in certain immunodeficiencies (4). In practice, treatment with a direct antifungal drug was combined with immunotherapy, aiming at immune restoration simultaneously with an elimination of the dermatophyte.

PATIENTS

The study includes 26 patients, 7 females and 19 males with CD caused by *Trichophyton rubrum*. Duration of disease was 3 to 45 years. Twelve patients were clinically and mycologically investigated at The Finsen Institute, 14 in the Rigshospital of Copenhagen. The age of the females at the time of the study varied between 35 and 70 years (mean 50.6 years) and the duration of their disease averaged 20.7 years. The males rangedin age from 24 to 66 years (mean 43.5 years), and the duration of symptoms averaged 13.0 years. Most of the patients developed symptoms in their twenties and thirties.

Associated conditions. One patient (4%) had allergic asthma and hayfever. Six (23%) reported atopy in parents or siblings. Seven males (27%) had dry skin of hands and feet prior to the fungus infection, in two complicated by an irritant contact dermatitis. Two patients had psoriasis vulgaris of the scalp, knees and elbows and one had pityriasis versicolor. Systemic diseases included one male with nefrolithiasis and one female with mild hypothyreoidism. Swimming was a frequent sport for 14 patients (54%). Two patients (8%) gave a family history of dermatophytosis in parents or siblings.

Clinical symptoms. The usual site of the chronic dermatophytosis was the plantar aspects of the feet (Table 1). One patient, had isolated lesions of the first, second and third right fingers, and four patients had infection confined to the toe nails and the toe webs. Eleven patients (42%) had the classical dry, scaling red palms with chalky furrows.

Previous treatment. 63% of the patients had received griseofulvin for more than one year and 29% for more than two years and all patients had been treated with a variety of topical antimycotics with slight success.

Controls. Controls in the lymphocyte transformation test, the crossed immunoelectrophoresis and the intradermal test were 33 females and 2 males from the staff. None had any history of dermatophytosis. The age range was 21 to 45 years with an average of 29.6.

METHODS

1. For clinical evaluation, a simple score system was used. Involvement of the feet with or without nails was indicated by +, while affection of both hands and feet with or without nails was scored as ++.

2. Mycological methods included microscopical examination of the skin and nail specimens using KOH and cultivation on Sabouraud dextrose agar 2% with cycloheximide and chloramphenicol. This examination took place pre-treatment and after 3, 6 and 12 months.

3. Blood tests: haemoglobin, leucocyte and differential count, platelets, glutamine/or oxalate/transaminase, alkaline phosphatase, creatinine and immunoglobulins A, G, M and E were examined initially and monthly during the year of investigation.

4. For the study of the cellular immune response, the lymphocyte transformation test (LTT) in vitro was carried out. The method had been reported previously (5, 6). In this study, mitogens included phytohaemagglutinin (PHA, Difco), poke weed mitogen (PWM, Gibco) and concanavalin A (Con A, Pharmacia) and antigens included purified protein derivate (PPD, Serum Institute of Denmark). *Candida albicans* (CA) and *Trichophyton rubrum* (TR). The CA and TR antigens were prepared as water-soluble extracts following a method earlier described (1). Prepared from a stock dilution of the extracts containing 10 mg protein per ml, a dilution of CA 1 : 100 and dilutions of TR 1 : 1 000 and 1 : 2 000 previously found optimal in the LTT in dose–response studies were used in the entire investigation. The same batch of CA and TR were used for the whole series. The lymphocyte transformation was measured by the incorporation of ^{14}C thymidin in a liquid scintillation counter. The results were based on triplicate cultures and expressed as increment counts per minute (Icpm), i.e. median counts per minute (CPM) in stimulated cultures minus median cpm for unstimulated control cultures. LTT was performed in all 26 patients at the end of a two month washout period without any topical or systemic antimycotic medication just prior to therapy. LTT was repeated three, six and 12 months after start of treatment i.e. four investigations per patient. The LTT was performed at 44 different occasions, each time including 2 to 4 patients and 2 controls.

5. In vivo evaluation of the delayed hypersensitivity was done with intradermal tests (IDT) using Tuberculin 1 unit per ml, TR dilution 1 : 1 000 equivalent to Dermatophytin 1 : 30 (Hollister-Stier), CA 1 : 100 and NaCl 0.9% as a negative control. For comparison, a group of 21 patients with chronic oral candidosis (COC), and a control group of 19 healthy individuals were tested. An immediate type reaction was a weal greater than 10 mm diameter at 20 minutes. A delayed type reaction was a papule or vesico-papule more than 7 mm in diameter at 48 hours. IDT was carried out at the first investigation date and 6 months later.

6. For evaluation of humoral immune responses to Trichophyton rubrum, crossed immunoelectro-

phoresis with intermediate gel (CIE) was used. The method was carried out as earlier described (7, 8). In this study the TR extracts was used as antigen and a pool of TR immune sera from rabbits as the reference serum. Patient serum for CIE was drawn from blood samples simultaneously with blood for LTT. Serum from seven patients was also investigated for specific IgE using crossed radioimmunoelectrophoresis (CRIE) (9).

7. Statistical comparisons of groups were made by the Mann-Wilcoxon non-parametric rank sum test. For comparison of frequencies Fisher's exact test was used. Friedman's multisample test was applied in the comparison of results from different investigation days.

Treatment. All patients were included in a double blind clinical trial with Levamisole or Placebo combined with griseofulvin throughout the year of study. Each patient received 1 g griseofulvin orally daily. Levamisole or placebo was given as tablets in a dose of 100–300 mg daily (according to weight) for two days each week.

RESULTS

The most important data are summarized in Table II.

1. Fourteen patients had tinea pedis alone with and without nail affection (score +) and 12 also had hand infection with and without nail involvement (score ++). Three patients discontinued Levamisole due to side effects: urticaria, an erythematous rash, and headache. The treatment was discontinued in one patient on placebo because of a flare up of psoriasis after two months of treatment. Two were lost to follow up after one and six months. Consequently, twenty patients were clinically and mycologically evaluable after one year. Eight of these had received griseofulvin plus Levamisole and 12 griseofulvin plus placebo. Five patients (62.5%) in the Levamisole group were clinically cured (one patient) or improved and seven (58%) improved in the placebo group while the remaining were unchanged. This result indicated no statistical difference in efficacy between the treatment schedules. The only patient who showed clinical and mycological cure was in the Levamisole group, but he relapsed 6 months after cessation of therapy.

2. Mycological examination at start revealed positive microscopy and T. rubrum by culture in all 26 patients. At the end of one year of follow up this was still true in eight patients, while a positive microscopy with a negative culture was demonstrated in seven patients and a completely negative mycology in five, of whom three had got Levamisole. No relation was found between clinical groups and results of mycological investigations.

3. All blood tests were normal apart from an isolated increase of serum IgM in one patient and elevation of IgM and IgE in five. Isolated increases of IgE alone were found in four patients. In six, total serum IgE was normal but specific IgE directed against *T. rubrum* was observed using CRIE (12).

4. Lymphocyte transformation in vitro (LTT). The results in the control group of 35, several of whom had been studied several times, were evaluated throughout the entire two years of the study. This period was divided in four sequential parts. The results from each

Table I. *Location of lesions*

	♂, $n=19$		♀, $n=7$	
Location	*n*	%	*n*	%
Palms, fingers	11	58	1	14
Finger nails	5	26	1	14
Soles	16	84	6	86
Toe webs	19	100	7	100
Toe nails	15	79	7	100

period were compared with those from the other three periods, individually and combined, each control being represented only by the first value from the period in question. There were no significant differences between the results in these four periods for any of the stimulants. Consequently, it was decided to use only one standard control group (SCG) for each stimulant in the comparisons with the various patient groups. The SCG consists of the first value obtained for each control giving 35 values for each stimulant.

For the patients, the following comparisons were made for each stimulant: (i) All patients versus SCG before treatment and after 3, 6 and 12 months (ii) Levamisole/Griseofulvin group (LGG) versus Placebo/Griseofulvin group (PGG) at 3, 6 and 12 months and (iii) all patient values from a given part of the study (0, 3, 6 and 12 months) versus all patient values from the other parts. With one exception, the responses to PHA, PWM, PPD, Con A and CA were normal at all investigation dates and there were no significant

Table II. *Review of patients 1 to 26, distribution of Levamisole and Placebo, extension of dermatophytosis, correlation to atopy, clinical and mycological results, and most important results of intradermal test (IDT) pretreatment (0) and after 6 months, lymphocyte transformation in vitro (LTT) pretreatment (0) and after 3, 6 and 12 months, crossed immunoelectrophoresis (CIE) and serum IgE*

Im = immediate, weal and flare type. Del = delayed hypersensitivity type. The results of IDT after six months only indicated if changes occurred. TR = *Trichophyton rubrum*. L = Levamisole. Pl = Placebo. (+) = hands *or* feet. (++) = hands *and* feet. P = in patients. F = in family.

Patients	Treatment	Clinical score	Atopy	Clinical evaluation at end of treatment	Mycology result 12 months		IDT TR 1 : 1 000	
					KOH	Culture	0	6
1. ♂ KR	L	+	P	Unevaluable (lost)	Pos	Neg	Im	
2. ♀ IH	Pl	+	No	Improved	Neg	Neg	Im + Del	Im
3. ♂ KO	L	+	No	Improved	Pos	Pos	Neg	
4. ♂ VJ	Pl	++	No	Improved	Pos	Neg	Neg	
5. ♂ HT	Pl	+	No	Improved	Pos	Neg	Del	
6. ♂ JS	Pl	++	No	Improved	Pos	Neg	Im	
7. ♀ RB	L	+	F	Unevaluable (rash)	Pos	Pos	Im	
8. ♀ NA	L	++	F	Improved	Pos	Pos	Neg	
9. ♂ VA	L	++	No	Unevaluable (lost)	Pos	Pos	Neg	
10. ♂ HJ	L	++	No	Cured	Neg	Neg	Im	
11. ♂ HO	Pl	++	No	Unevaluable (psoriasis)	Neg	Neg	Neg	
12. ♂ FM	L	+	No	Improved	Neg	Neg	Neg	
13. ♀ KV	Pl	+	No	Unchanged	Pos	Pos	Neg	Im
14. ♂ HB	Pl	++	F	Improved	Neg	Neg	Neg	Del
15. ♀ BM	Pl	+	No	Improved	Pos	Neg	Del	
16. ♀ GM	L	+	No	Unevaluable (urticaria)	Pos	Pos	Im	
17. ♂ AG	Pl	+	No	Improved	Pos	Pos	Im	
18. ♀ BH	L	+	F	Unchanged	Pos	Neg	Im	Del
19. ♂ KL	Pl	+	No	Unchanged	Pos	Pos	Im	Im + Del
20. ♂ SM	Pl	+	F	Unchanged	Pos	Pos	Im	
21. ♂ PL	L	++	No	Unevaluable (headache)	Pos	Pos	Neg	
22. ♂ EB	L	+	F	Unchanged	Pos	Pos	Neg	Del
23. ♂ JH	L	++	No	Improved	Neg	Neg	Del	Neg
24. ♂ EJ	Pl	++	No	Unchanged	Pos	Neg	Im	Del
25. ♂ ET	Pl	++	No	Unchanged	Pos	Neg	Im	Im + Del
26. ♂ GA	L	++	No	Unchanged	Pos	Pos	Neg	

differences between the groups. Patient no. 26 had a low response to PHA. He was followed throughout the year of investigation and did not improve either in LTT, nor clinically or mycologically in spite of being treated with Levamisole.

Stimulation with TR in both dilutions showed that lymphocytes from the patients as a group responded more strongly than those from the controls (Fig. 1) at all four investigation dates. All differences were significant (p=0.003, 0.001, 0.001, 0.003 for TR 1:1 000, p=0.01, 0.002, 0.00003, 0.00008 for TR 1:2 000). Thirteen patients (50%) responded at the first investigation day with an ICPM<1 000 using TR 1:2 000 and may be considered low responders. Ten of these had been scored clinically with + and three with ++. In contrast, nine patients with clinical score ++ and only four with + had ICPM>1 000 viz. strong responders. This association between response and clinical score is significant (p=0.024). In the control group, three persons (9%) had ICPM>1 000. During the follow-up period 11 of 12 retested low responders showed ICPM>1 000 using TR 1:2 000 at one or more occasions, while this was the case for only five of 32 retested low responder controls (p=0.000006). There was no correlation between the increased ability to respond to TR 1:2 000 and treatment with Levamisole. Retesting of 12 strong responders showed ICPM<1 000 in 7 patients on one or more occasions, while five patients were strong responders at each investigation. Only one patient (no. 26) had a constantly low response. No differences were found between the LGG and PGG throughout the year of follow-up.

LTT TR 1:2 000 ICPM				CIE TR	Hyper IgE
0	3	6	12		
2 328	3 620	ND	ND	Neg	Yes
986	573	1 446	2 238	Neg	No
170	2 042	2 396	329	Pos	No
9 348	658	805	749	Neg	No
281	1 653	2 249	786	Neg	No
277	1 415	58	1 062	Pos	Yes
614	ND	ND	ND	Neg	No
746	11	1 177	458	Pos	Yes
1 823	ND	ND	ND	Neg	No
3 129	238	2 786	2 136	Neg	No
2 127	1 014	ND	ND	Pos	No
1 387	100	44	598	Pos	No
504	330	1 838	298	Neg	No
1 677	ND	1 497	5 610	Pos	No
256	1 801	447	1 227	Neg	Yes
22	2 164	1 340	ND	Neg	Yes
1 293	1 319	1 717	667	Neg	Yes
76	1 353	1 085	1 513	Pos	No
1 275	ND	ND	6 377	Pos	Yes
176	1 087	456	939	Pos	No
3 247	1 966	661	ND	Pos	Yes
460	1 290	1 108	268	Neg	Yes
2 444	ND	2 302	134	Neg	Yes
3 211	2 376	3 539	2 956	Neg	No
3 750	ND	625	1 730	Pos	Yes
165	ND	37	468	Neg	Yes

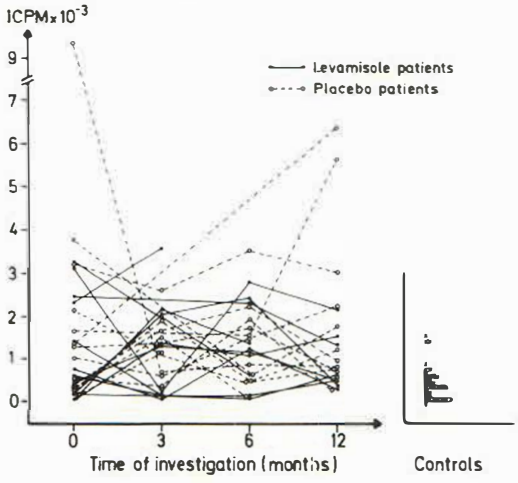

Fig. 1. Lymphocyte transformation in vitro in chronic dermatophytosis by *T. rubrum* (dilution 1:2000). Follow-up study. ICPM = increment counts per minute.

especially, there was no tendency of increased stimulation ability in the LGG. To investigate if there were any fluctuations over the entire year, the results from 19 patients, who underwent all four examinations were analyzed by Friedman's multisample test. We found no significant variations from date to date for any of the mitogens or antigens, including TR.

5. Intradermal test (IDT). Results of IDT are given in Table III. With TR 1:1 000 as test material, immediate reactions were observed in 11 (42%) of the CD patients and in 2 (10%) of the COC patients, while no immediate reaction were seen in the control group ($p=0.0008$). Delayed reactions, however, were seen equally often (12, 14 and 16%) in the CD, COC and control groups. Immediate followed by delayed response was seen only in one patient with CD. Twenty-three of the patients were retested after six months. The response was unchanged in 15 patients, while three in the LGG and six in the PGG showed a different response (Table II). There was no correlation between a change to delayed type and improvement or treatment with Levamisole. With CA 1:100 as antigen, no immediate reactions were seen in the CD group. Two (11%) of the controls responded in this way, while 9 (43%) of the COC patients showed this reaction to CA ($p=0.03$; unpublished results). Nineteen (73%) of the CD patients had a delayed reaction to CA. IDT with PPD 1

Table III. *Results of intradermal test with T. rubrum (TR 1:1000), C. albicans (CA 1:100) and Tuberculin (PPD 1 u/ml)*

COC = chronic oral candidosis. CD = chronic dermatophysis caused by *T. rubrum* and C = controls

Antigen	TR 1:1 000			CA 1:100			PPD 1 u/ml		
Group ...	CD	COC	C	CD	COC	C	CD	COC	C
Number ...	26	21	19	26	21	19	26	21	19
Reactions (%)									
Immediate	42	10	0	0	43	11	0	0	0
Delayed	12	14	16	73	33	63	77	81	84
Mixed	4	0	0	12	0	21	0	0	0
Negative	42	76	84	15	24	5	23	17	16

u/ml revealed no differences between the groups. Six patients with CD had negative response. Five of these were retested and found positive (delayed response) while one was lost to follow-up.

6. Crossed immunoelectrophoresis (CIE). Humoral antibodies specifically directed against TR were demonstrated in 11 of the CD patients but in none of the controls. Five of these patients were in the clinically less affected group (35%) while six came from the group with multifocal lesions (50%) showing that there is an insignificant tendency for patients with wide-spread lesions to develop IgG antibodies. The presence of raised total serum IgE or specific IgE against TR demonstrated by CRIE could not be correlated to the ability to produce IgG (Table II).

DISCUSSION

An atopic background has previously been discussed as being of some importance for the development of chronic *T. rubrum* infection (1, 2, 3). Twenty of the 26 patients in this study had either clinical atopic disease and/or were found to have raised serum IgE and/or reacted with an immediate weal to TR antigen. Thus, in the widest sense of atopy 77% were atopic individuals. Although similar data are not available for the background population, this seems an extraordinary high frequency. An atopic state is generally believed to be at least in part genetic, but chronic TR infection does not appear to have a strong genetic element: Only two of our patients had a family history of this condition. Moreover, we have found no association between HLA and chronic TR infection in CD patients (10).

More than half of the patients were frequent swimmers and a further 27% had a defect in the skin barrier due to irritant hand dermatitis at the time of onset of their disease, pointing to the role environmental factors play in the pathogenesis.

The lymphocyte studies in vitro revealed no general immunodeficiency except in one patient (no. 26). As Levamisole is considered an immunostimulant only in the immunodepressed organism, increased lymphocyte responses in these patients were not expected and not found. Even in patient not. 26, who got Levamisol no increase in the responses to mitogens or antigens was observed. Using the specific TR antigen, a considerable variability both in the group and in the individual patient was found. All the patients except no. 26 at one or more occasions showed a definite response to TR. In spite of the great variability, the specific TR responses were significantly higher in the patients than in the control group, indicating that the majority of the patients had circulating TR-reactive lymphocytes. Before treatment, high responsiveness to TR correlated significantly to the extent of the lesions indirectly indicating a correlation between the antigenic load and the in vitro response. In contrast to our previous study of patients with acute dermatophytosis (6), who experienced an increased responsiveness during the first months of treatment, no significant changes were seen during treatment in the present group of chronic disease. There was no correlation between the in vitro response and the clinical result, probably because complete elimination of the antigen did not occur. Only three patients (nos. 14, 10, 24) showed constantly high ICPM to TR, one of whom improved, while two were clinically unchanged. Taken together, these results of LTT indicate that impaired lymphocyte responses, whether non-specific (mitogens) or specific (TR antigen), are not a major cause of chronic dermatophytosis.

In almost half of the patients (42%), specific humoral antibodies to TR were detected. The significance of IgG antibodies in CD is unclear. A blocking effect by autologous antibody-containing serum on the TR stimulation of the lymphocytes in those patients, who had high responses to TR in the LTT could not be demonstrated (unpublished

observations). Intradermal tests with TR showed that most patients with CD reacted either with an immediate reaction weal (42%) or not at all (42%), while only 12% had a delayed reaction. This finding is in contrast to the results of IDT in 15 patients with acute dermatophytosis (6). It is noteworthy that a high frequency of weal reaction to the specific antigen was also observed in patients with COC. This observation supports the notion that the weal and flare reaction is the result of long-lasting constant exposure to the antigen (11). The pattern of reaction to IDT could not be related to responsiveness in LTT. Delayed reaction to both CA and PPD was found in most of the CD patients (73% and 77%) confirming that these patients generally have a normal cell-mediated immune response. The treatment had dubious success, and it seems that Levamisole has no effect in chronic TR infection, at least not in this group of generally immunocompetent patients.

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