Assessment of the Treatment Protocol Described in the Guidelines for *Trichophyton tonsurans* Infection

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Abstract

Background: Infection with the anthropophilic fungus *Trichophyton tonsurans* has spread among members of combat sports clubs and has become a serious public health problem in Japan and other countries. Infection usually provokes only a weak inflammatory response, and treatment compliance tends to be poor.

Objective: To evaluate the hairbrush method and the treatment protocol described in the guidelines for *T. tonsurans* infection.

Method: The study subjects were 69 individuals with positive hairbrush culture from among 327 members of 12 judo clubs participating in the survey. (a) Subjects with no more than 4 colonies by the hairbrush method were treated with miconazole nitrate shampoo. (b) Subjects with 5 or more colonies were treated with (1) itraconazole at a dose of 100 mg/day for 6 weeks or at a dose of 400 mg/day for 1 week, or (2) terbinafine at a dose of 125 mg/day for 6 weeks or at a dose of 500 mg/day for 1 week. Treatment efficacy was monitored by the hairbrush method at 1.5 and 3 months after treatment.

Results: Of the 46 subjects with 5 or more colonies isolated by the hairbrush method, 32 (69.6%) took itraconazole or terbinafine in compliance with their treatment schedules and were negative for *T. tonsurans* after treatment. Of the 23 subjects with 4 or fewer colonies, 15 (65.2%) were negative for *T. tonsurans* after treatment with miconazole nitrate shampoo.

Conclusion: The treatment protocol seems promising, but poor compliance is a problem with the oral treatment regimens. The shampoo therapy is only partially effective, with 35% of subjects remaining positive for *T. tonsurans* after this therapy. In order to eradicate this disease, we have renewed the guidelines for *T. tonsurans* infection.

Key words: *Trichophyton tonsurans*, tinea capitis, hairbrush method, follow-up study, anti-fungal therapy, guidelines

Infection with *Trichophyton tonsurans*, the major pathogen causing tinea capitis in Europe and America¹³, is becoming a serious public health concern in Japan⁴⁴. Outbreaks of *T. tonsurans* are now emerging among members of combat sports clubs in Japan, with one infection after another reported since 2001¹¹. To date, the infection has not been well controlled in Japan, nor is there yet a consensus on the most effective methods of prevention or treatment. Since the causative organism is an anthropophilic fungus, infection tends to provoke only a weak inflammatory response¹². Consequently, patients tend to comply poorly with treatment schedules and discontinue treatment prematurely. Insufficient knowledge on the part of patients and their families, as well as inadequate public awareness of the disease, hamper efforts to control it¹⁰. 

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In an earlier study using the hairbrush method\textsuperscript{13}, we performed a survey of members of many Judo clubs all over Japan at their request and reported that about 12% of the members tested positive for \textit{T. tonsurans} infection\textsuperscript{13}. Subjects with positive hairbrush test results were prescribed treatment and were re-tested after 3 months. Here we report the results of the follow-up study. To eradicate this infection, it is very important to determine the most effective method of treatment.

**METHODS**

**Study design**

As described earlier\textsuperscript{13}, we performed a survey to assess the incidence of \textit{T. tonsurans} infection in judo club members in Japan from November 2002 to August 2004, using methods: In some cases, at the request of the club, the survey using the hairbrush method was conducted at the club site by a visiting staff member from our dermatology clinic. Otherwise, we sent questionnaires and hairbrushes by mail to clubs located throughout Japan and asked the members to perform the test with one another and return the questionnaires and hairbrushes.

Participants with positive test results (indicating \textit{T. tonsurans} infection) were treated according to the treatment protocol described in a leaflet\textsuperscript{15,16} and monitored using the hairbrush method to determine the treatment efficacy until this method became negative. The usual direct KOH test or culture of hair or scales was not used for the monitoring.

**Study population**

Three hundred twenty-seven participants (280 males and 47 females) from 12 clubs continued in follow-up after the initial survey. The study population consisted of the 69 individuals who had tested positive by the hairbrush culture in the earlier survey\textsuperscript{13}. The study was approved by the local ethics committee, and written informed consent was obtained from each subject.

**Methods**

Participants from clubs near our clinic (37 participants from 4 clubs) were treated at our clinic, while those from clubs farther away (32 participants from 8 clubs) were referred for treatment to clinics in their area. Treatment was prescribed according to the number of colonies isolated and the treatment guidelines proposed previously\textsuperscript{16}. In brief, subjects with tinea corporis were treated with topical antifungal agents for a minimum of 1 month. Treatment of these participants was based on the number of colonies isolated by the hairbrush method. Those with 4 or fewer colonies were instructed to wash their hair with a miconazole nitrate shampoo daily for 3 months. Participants with 5 or more colonies were treated either (i) with itraconazole at a dose of either 100 mg/day for 6 weeks\textsuperscript{17} or 200 mg/day for 1 week, or (ii) terbinafine at a dose of either 125 mg/day for 6 weeks\textsuperscript{18} or 500 mg/day for 1 week\textsuperscript{19}.

For all participants, treatment efficacy was monitored by the hairbrush method at 1.5 and 3 months after treatment. Screening by the hairbrush method was also performed after 6 and 12 months as necessary.

In addition to pharmacotherapy, emphasis was also placed on lifestyle guidance. The participants were instructed to clean their club rooms and their houses with a vacuum cleaner daily, wash the clothing used in a match, always shower after training, refrain from sharing towels or personal hygiene items with other club members, perform frequent screening to detect eruptions early, and refrain from participation in a match if eruptions were present\textsuperscript{19}.

**RESULTS**

**Demographics**

Classification of the 69 study participants based on the number of colonies isolated by the hairbrush method showed 23 with 4 or fewer colonies and 46 with 5 or more colonies. In responses to study questionnaires, 46 (66.7%) of the participants indicated that they had friends with tinea corporis, and 49 (71.0%) acknowledged a personal history of tinea corporis. Thirty-three participants (47.8%) reported having tinea corporis at the time of the survey (Table 1).

**Treatment for participants with 5 or more colonies isolated by the hairbrush method**

The 46 participants with 5 or more colonies by the hairbrush method were instructed to take oral systemic drugs according to the treatment guidelines\textsuperscript{16}. Seven participants (15.2%) did not visit a clinic and did not receive treatment at that time.

The treatment regimens given to the remaining 39 subjects were as follows: pulse therapy with terbinafine (500 mg/day for 1 week), 14 subjects; continuous treatment with terbinafine (125 mg/day for 6 weeks), 16 subjects; pulse therapy with itraconazole (400 mg/day for 1 week), 8 subjects; and continuous treatment with oral itraconazole (100 mg/day for 6 weeks), 1 subject.

Thirty-two subjects completed their treatment. Of
Table 1. Demographics of the 69 study participants

| Male sex | 67 (97.1%) |
| Mean age ± SD (range), in years | 18 ± 2.7 (12 – 27) |
| Mean height ± SD (range), in cm | 170 ± 5.3 (156 – 184) |
| Weight ± SD (range), in kg | 77 ± 14.7 (55 – 125) |
| Mean no. of colonies isolated by hairbrush culture (range) | 8.6 ± 27.7 (1 – 126) |
| No. of participants (%) classified by hairbrush culture results | |
| No. with 1 ~ 4 colonies (%) | 23 (33.3%) |
| No. with 5 ~ 50 colonies (%) | 27 (39.1%) |
| No. with > 51 colonies (%) | 19 (27.5%) |
| Positive questionnaire responses (no. of participants, %) | |
| infected family member | 46 (66.7%) |
| history of tinea corporis | 49 (71.0%) |
| increased dandruff | 12 (17.4%) |
| concomitant tinea corporis | 33 (47.8%) |

Table 2. Systemic treatment results by regimen

<table>
<thead>
<tr>
<th>Participants with ≥ 5 colonies by hairbrush culture (n=46)</th>
<th>Treatment Regimen</th>
<th>Treatment Parameter (n=46)</th>
<th>Completed (n=32)</th>
<th>Discontinued (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic treatment (n=39)</td>
<td>TBF 500mg/day × 1 wk</td>
<td>14</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TBF 125mg/day × 6 wks</td>
<td>16</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>ITZ 400mg/day × 1 wk</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>ITZ 100mg/day × 6 wks</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No treatment (n=7)</td>
<td></td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Negative results at 3 months after treatment</td>
<td></td>
<td>32/46 (69.6%)</td>
<td>32/32 (100%)</td>
<td>0/14 (0%)</td>
</tr>
</tbody>
</table>

Abbreviations: TBF, terbinafine; ITZ, itraconazole.

these, 30 tested negative for *T. tonsurans* by the hairbrush culture method at 15 months after the start of the treatment and all 32 treatment-adherent participants were negative at 3 months.

Seven subjects chose to discontinue treatment. Four subjects who were treated with itraconazole pulse therapy reported discontinuing the drug due to feelings of weakness, and the remaining three subjects who underwent continuous treatment with terbinafine did not provide a reason. None of the participants who discontinued oral treatment prematurity at their discretion gave negative tests (Table 2).

The 7 participants who declined treatment initially and the 7 who chose to discontinue treatment were advised to receive treatment again. After 6 to 12 months, half of these participants were found to be negative by the hairbrush method.

**Treatment for participants with 4 or fewer colonies isolated by the hairbrush method**

Twenty-three participants had 4 or fewer colonies isolated by the hairbrush method and were instructed to use a miconazole nitrate shampoo according to the treatment guidelines46. After 3 months, 15 participants (65.2%) tested negative for *T. tonsurans*, and 6 (26.0%) tested positive, with an increased number of colonies. Two participants (8.7%) were lost to follow-up.

**Safety results**

Hematology tests revealed no abnormalities before, during or after treatment in any subjects who received oral anti-fungal drugs.

**DISCUSSION**

In Japan as well as elsewhere, outbreaks of *T. tonsurans* infection are increasing, mainly among members of combat sports clubs35. Likely explanations for the spread of this disease include (1) the prevalence
of asymptomatic carriers, who remain untreated; (2) failure to recognize and diagnose the infection in daily dermatology practice, and (3) misdiagnosis of the disease as eczema and treatment with topical steroids, leading to disease exacerbation\(^{11}\).

There are estimated to be approximately 500,000 judo athletes and 30,000 wrestlers officially registered in Japan. We distributed education leaflets to combat sports clubs all over the country\(^{16}\) and advised them to participate in a survey using a questionnaire and the hairbrush method. Participants with positive results were treated according to the treatment protocol we prepared.

For systemic treatment, subjects were given oral itraconazole or oral terbinafine, administered either in a 1-week pulse-dose regimen or a 6-week continuous-dose regimen\(^{21}\). Our dermatology clinic recommends the pulse-dose regimen for both these drugs\(^{16}\). This regimen was the preferred option in this study because it seemed difficult for athletes to continue taking a drug for as long as 6 weeks, it is easy to administer therapy with high compliance\(^{15,20}\), and it can improve the quality of life of the patient\(^{16}\). However, the continuous-dose regimen was allowed as an alternative because the pulse-dose regimen is not widely used by general dermatologists in Japan and because pulse therapy with terbinafine\(^{15,22}\) is not covered by the health insurance system. We indicated the dose of itraconazole pulse therapy of 200 mg/ day for 1 week in guideline\(^{16}\) in 2003, because the itraconazole pulse regimen of 400 mg/ day for 1 week was formally approved in 2004 in Japan. Eight cases were treated with the latter itraconazole pulse therapy after the approval.

In the present follow-up study, 46 participants had 5 or more colonies isolated by the hairbrush method and 32 (69.6\%) of these took oral drugs according to the protocol guidelines. Hairbrush culture screening performed at 3 months after treatment showed these participants to be negative for \textit{T. tonsurans}. This finding suggests oral treatment regimens are effective in eradicating this infection.

Compliance with the treatment recommendations was very poor, as some participants did not visit a clinic and others chose to discontinue their medication prematurely. Those who did not adhere to their treatment schedules remained positive for \textit{T. tonsurans} following treatment.

The protocol specified that patients with 4 or fewer colonies should be treated with a miconazole nitrate shampoo\(^{16}\). We classified patients by this criterion in order to eliminate false-positive cases, in which \textit{T. tonsurans} has not infected but has only attached to the hair. Miconazole nitrate shampoo was developed for the treatment of seborrhoeic dermatitis and is the only anti-fungal shampoo available in Japan. There have been no clinical studies of this product for the treatment of tinea capitis, but it is believed to be effective for the prevention of infection, based on experiments using stratum corneum of healthy human heel or guinea pig skin\(^{23}\). Another anti-fungal agent, ketoconazole, was reported to cure tinea capitis in 33\% of patients when used alone\(^{24}\), but a ketoconazole shampoo is not available in Japan.

Participants with 4 or fewer colonies isolated by the hairbrush method were treated with a miconazole nitrate shampoo alone. Of the 23 participants, 14 (61\%) were negative for \textit{T. tonsurans} after treatment, but the remainder had an increased number of colonies. This finding underscores the necessity of careful patient follow-up and indicates that the treatment efficacy of miconazole nitrate shampoo needs to be further investigated. Perhaps the cut-off number (i.e., 4 colonies isolated by the hairbrush method) specified in our protocol should be reduced, and more participants should be treated with systemic therapy.

In conclusion, we evaluated the efficiency of our treatment protocol\(^{16}\). As a result, we found a need to revise the guidelines for \textit{T. tonsurans} infection, including dosage of itraconazole for pulse therapy according to the health insurance system, and the title “for gladiator” because \textit{T. tonsurans} infection has spread not only among judoists. Now we have been investigating a new protocol reducing the cut-off number from 4 to 2, to treat with systemic therapy for participants with 3 or more colonies isolated by the hairbrush method\(^{21}\).

References