Clinical study

MYCOSES IN CHILDREN
SYSTEMIC TREATMENT*

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ABSTRACT

Report of experiences in treating childhood onychomycosis (caused by *Trichophyton rubrum*) in 12 children. Treatment with itraconazole 200 mg once daily for 12 weeks, revealed clinical and mycological cure in 10 children within 2-4 months. In one child no cure could be obtained, another one failed to appear for the follow-up.

In 31 children with tinea capitis caused by *Microsporum canis* (microsporosis) systemic oral treatment was performed using itraconazole. The drug was administered as a solution once daily with a meal, in a dosage of 5 mg/kg bodyweight.

In all 31 children with an average of 5,7 years, cure could be obtained in 6,1 weeks (standard aberration about 2 weeks).

In conclusion, systemic treatment with oral antifungals is effective and safe in childhood onychomycosis and tinea capitis. In our experience the azoles seem to be the drug of choice in the management of scalp infection due to *Microsporum canis* in children. Side effects using itraconazole were mild and transient.

KEY WORDS

childhood onychomycosis, tinea capitis systemic treatment, oral antifungals, azoles, itraconazole

INTRODUCTION

Cutaneous mycoses in children occur in immunocompetent individuals as well as in those with primary or secondary immunodeficiencies, and account - according to references - for 7 - 15% of disorders seen in a pediatric clinic (1).

Common fungal infections in children are mucocutaneous candidiasis, tinea pedis, tinea corporis, tinea capitis, onychomycosis and to a lesser extent pityriasis versicolor.

Risk factors include prolonged systemic corticosteroid or antibiotic therapy, use of chemo-therapeutic agents, transplant recipients, HIV infection, but in many instances in our cases an infected family member may be found - mainly in the condition of onychomycosis.

Mycotic presentations in children are generally similar to adults, but can occasionally be atypical, and a diagnostic and therapeutic challenge.

Therapeutic strategies in children differ from adults because topical rather than oral therapy is preferred. Oral therapy is required for those with tinea capitis, in the majority of onychomycosis patients, and in immunocompromised patients.

Until recently, griseofulvin has been the standard oral agent in children due to its high safety and

**This contribution has been delivered as a plenary lecture at the Symposium on Dermatomycoses and Parasitic Skin Diseases, Ljubljana, June 5-6, 1998.*

tolerability profile. The new antimycotics - the triazoles and terbinafine are interesting new substances that offer new treatment options (1).

The present commmunication is dealing with fungal infections in children, which required systemic antifungal treatment. it is primarily centered on onychomycosis and tinea capitis.

CHILDHOOD ONYCHOMYCOSIS

Onychomycosis is rare in healthy children, but HIV infection, Down's syndrome, long-term systemic corticosteroid treatment, tinea pedis and tinea capitis increase the risk of infection (1). Although there is some evidence that a positive family history increases the risk of onychomycosis, it is unclear, if this is due to chronic exposure to the pathogen or to an undefined genetic immunodeficiency- Zaias as well as some other authors estimate an autosomal dominant pattern for this condition (2).

Concerning onychomycosis in children there are only a few studies available (3). The prevalence of onychomycosis in children from surveys conducted in different parts of the world may range from 0 - 2.6% (thus, the prevalence of onychomycosis in adults may be approximately 30 times that of children). Those facts may raise the question about the reason for lower prevalence of onychomycosis in children than in adults: it may be possibly because of reduced exposure to fungus with less time spent in environments which may have a high density of infective hyphae and spores, because of faster nail growth compared to the older populations, because of smaller surface area of nail available for attack by onychomycosis, because of reduced likelihood of trauma and subsequent colonization and last but not least because of reduced prevalence of tinea pedis in the younger age group (3).

Clinical presentations are similar to adult disease. In nearly all studies - as in ours - *Trichophyton rubrum* is the predominant organism.

Also in childhood onychomycosis topical therapies have generally been ineffective, particularly when there is significant nail plate disease or nail matrix involvement.

The new oral antifungals like fluconazole, itraconazole, and terbinafine seem in the treatment of onychomycosis in children to be generally effective and well tolerated, but strategies and suggested dosage regimen are of limited experience in children up to date.

With *terbinafine* weight-dependent dosage for treatment of children is established, but for treatment of onychomycosis no fixed treatment-schedules are available.

For treatment of onychomycosis with *itraconazole*-capsules 5mg/kg bodyweight for *continuous therapy* is recommended, whereas itraconazole suspension only 3mg/kg bodyweight has to be given - in treatment with suspension more gastrointestinal upset is seen. For *pulse dosing* 100mg itraconazole twice daily given for one week each month - for 3 cycles - may be effective.

For treatment with *fluconazole* 3-6mg/kg bodyweight is recommended, but there is no experience neither concerning continuing nor pulse-treatment in childhood-onychomycosis.

Let me report *on our first experience* in treating childhood onychomycosis in 12 children with clinically and mycologically confirmed long-standing severe onychomycosis of distal subungual type due to *Trichophyton rubrum* (4). In all cases toenails were affected and in one girl fingernails as well. In 4 children onychomycosis was accompanied by significant onychodystrophy. Age of the children ranged between 10 and 17, 6 were males and 6 were females. Four children were siblings, two of them twins. Two children have failed to respond to treatment with griseofulvin as well as terbinafine, and another child to surgical removal of the nailplates.

All children were started on itraconazole 200mg once daily for 12 weeks.

RESULTS

Within 2 - 4 months, a clinical and mycological cure was achieved in 10 children. One child failed to come to the follow-ups and in another one no cure could be obtained within 5 months.

Routine monitoring of laboratory tests during treatment did not reveal any abnormalities, no side effects were observed. All cases were followed and in the cured no recurrences were detected up to now. In conclusion: in our experience cure seems to be achieved in a shorter time in children than in adults, in addition severe dystrophic nail changes cleared completely. To confirm specific pediatric requirements further studies are needed.

TINEA CAPITIS

Tinea capitis is the most common of all cutaneous mycoses in children and remains a significant public health concern all over the world.

In the past 40 years a dramatic change in the species of dermatophytes isolated from children with

tinea capitis has occurred - in Europe as well as in the United States. In general, fungi causing tinea capitis show geographical specificity - the predominant organism varies from continent to continent. In Europe *Microsporum canis* is most common at present. In the US the nonfluorescent and endothrix *Trichophyton tonsurans* is seen in about 90% mainly in urban areas. Also there is an increase in the UK and Australia. *Microsporum ferrugineum, Trichophyton violaceum*, as well as *Trichophyton schönleinii* are seen worldwide (5).

CLINICAL FEATURES

The clinical appearance of tinea capitis depends mainly from the infective agent and may be different. Inflammatory tinea capitis may have multiple clinical forms - Kerion celsi is the most common variety presenting an intense, painful suppurative reaction and is invariably associated with cervical lymphadenopathia (Fig. 1).

Non - inflammatory (or "dry") tinea capitis may

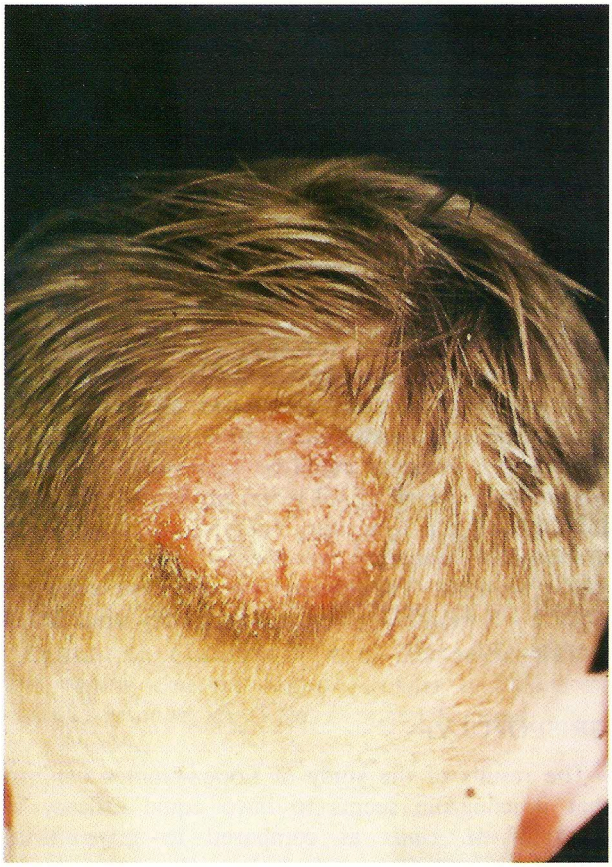

Figure 1. Kerion celsi.(inflammatory tinea capitis).

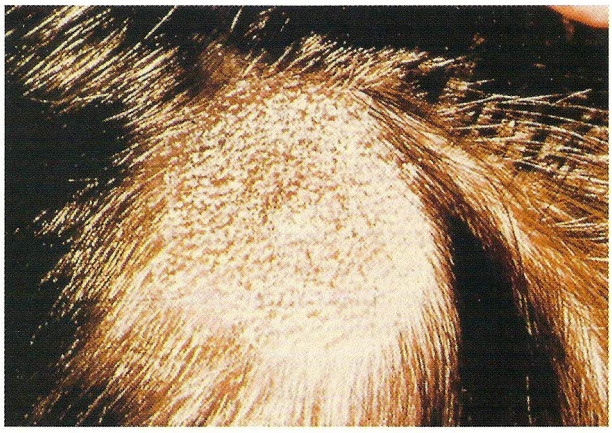

Figure 2. Noninflammatory (or "dry") tinea capitis: Microsporosis.

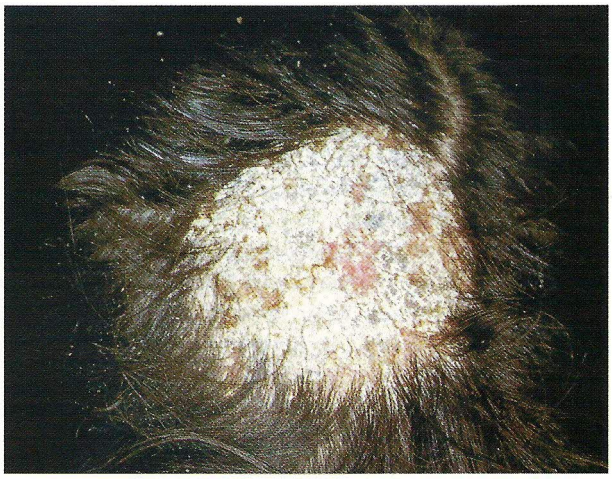

Figure 3. Favus: Formation of so-called "scutula".

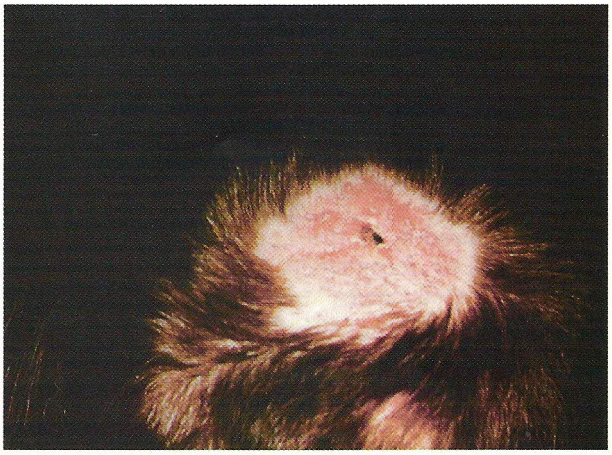

Figure 4. Misdiagnosed tinea capitis: scarring alopecia may result.

resemble "gray - patch scaling" like in microsporosis (Fig. 2) or so called "black-dot tinea capitis" - typically observed in *T. tonsurans* infections.

Favus - mainly caused by *Tr. schönleinii* - is a special clinical entity with formation of so-called "scutula" (Fig. 3) (5).

If the condition of tinea capitis is misdiagnosed or left untreated, scarring alopecia may result (Fig. 4).

Special importance of tinea capitis as significant public health arises from the fact, that in *Microsporum canis* and *Trichophyton tonsurans* the possibility of colonization, i.e. an asymptomatic carrier state (including both children and adults), has to be considered (5).

The second reason of public health concern is the fact that the condition is spread easily among family members, classmates, infants in day-care centers and may also be transmitted via infected fomites like hats, combs, towels or telephones and so on (5). Furthermore infective fungal elements can survive for long periods of time - the viability of dermatophytes in hair is estimated for up to 2 years. These circumstances may raise doubt if eradication of tinea capitis is really feasible!

Management of tinea capitis has always been a problem. Since 1958, oral griseofulvin has been the standard treatment for tinea capitis caused by dermatophytes, mainly Microsporum species. Infection often cleared slowly, sometimes requiring several months for complete resolution. In patients, who failed to respond or were unable to tolerate griseofulvin, ketokonazole was the only alternative therapy (1). Itraconazole as well as fluconazole and terbinafine are promising new drugs on the horizon, but only terbinafine is licensed for oral treatment in children at present. Suggested dosage as well as treatment schedules depend on the type of infection.

With *itraconazole* a daily dose of 5mg/kg bodyweight given continuously for a time of 4 weeks or in a pulse regimen may be effective (5). *Terbinafine* in a weight-dependent dose given for 1 to 8 weeks may also be superior to griseofulvin (5). Little experience has been gained with *fluconazole,* with the exception of one publication in the Lancet (6). The problem with all these recommendations is the fact that larger controlled clinical trials are not available.

Our first experience with itraconazole in that field was obtained by administration of itraconazole to 31 children (7). 12 males and 19 females with an average age of 5.7 years suffering from tinea capitis due to *Microsporum canis* in a clinical open, non-randomized trial.

Itraconazole was administered as a solution once daily with or after a meal in a dosage of 5mg/kg bodyweight. All children were followed up in a 2-weekly interval. Itraconazole was administered until mycological investigation (i.e. native specimen as well as cultivation) revealed negative.

RESULTS

Cure could be achieved in an average time of 6.1 weeks (standard aberration of about 2 weeks). According to age groups, duration of treatment will depend on the age of the affected diseased children; i.e. little children will need a shorter time of therapy for cure than older children. Side effects were mild and transient (mild diarrhoea and gastrointestinal upset in each one child, transient rush in two children at the beginning of therapy - possibly a mycid reaction).

To give a definite answer to the question about the best *agent for the management of tinea capitis* in children some *references* should be analyzed.

ITRACONAZOLE

Retanda carried out treatment in 20 children for a period of 30 days with a dosage of 100mg itraconazole daily. At the end of treatment complete clinical and microbiological cure was observed in 6 cases; but 9 children were cured in 2 weeks, and 5 in 4 weeks after discontinuation of treatment (8).

Some authors showed interesting results also by *low dose* individually adjusted therapy to body weight although the duration of therapy was longer: Legendre reports on 50 patients with tinea capitis treated with itraconazole 25 - 100 mg/day for 20 to 73 days (3 - 10 weeks) (7 studies carried out in 6 countries). As a result an overall cure in 93% microbiologically and in 75% clinically could be achieved (9). Lukacs reports on 3 siblings (3 - 8 years) previously unsuccessfully treated for 5 months. Therapy was changed to itraconazole 33mg/day; treatment duration was 5, 7 and 8 months. The children were cured clinically after 2 - 5 months and microbiologically after 5 - 8 months (10).

GRISEOFULVIN

The results of the study of Lopez-Gomez confirm that itraconazole seems to have equal efficacy in cases of *M. canis* as compared to griseofulvin: clinical as well as mycological results were almost identical for both drugs. But itraconazole appeared to be better-tolerated (11).

TERBINAFINE

Only a few data on treatment of tinea capitis due to *M. canis* are available to date.

In an open clinical pilot study in dry noninflammatory tinea capitis Haroon could achieve a cure in about 80%, but the causative agents have not been *M. canis* (12). In a later publication Haroon was able to show that the duration of treatment will not influence the cure-rates to a great extent (therapy for 1, 2 or 4 weeks revealed no difference between treatment-duration of 2 or 4 weeks), but the etiologic agents again have been *Tr. violaceum* and *Tr. tonsurans* (13).

Nejjam found encouraging cure rates in children suffering from tinea capitis due to *Tr. violaceum* and *Tr. schönleinii*, but not in *M. canis* infections (14). And finally, the results of Dragoš in treatment of tinea capitis due to *Microsporum canis* with terbinafine showed the difficulties in tretment of tinea capitis due to *Microsporum canis* (15).

CONCLUSION

In sum, according to our experience the azoles would be the drug of choice in the management of tinea capitis due to *Microsporum canis*.

Principles in treatment of tinea capitis could be defined as follows:

I. "Any child with a scaling scalp or alopecia should be considered to have tinea capitis!"

II. Recommendation to take samples for cultivation from all family members in order to detect latent infections.

III. The need for higher doses for short duration is based on our experience.

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