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Original Article

Fungal Nail Infections in Tehran, Iran

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Abstract

Background: Onychomycosis results from invasion of the nail plate by dermatophytes, yeasts or mould species of fungi. The objective was to determine the etiological agents of onychomycosis.

Methods: A total of 549 patients clinically suspected of onychomycosis were examined for causative fungal agents. Both direct microscopy and the cultures of the nail material were performed to identify the causative agents between 2004-2005 in Tehran, Iran.

Results: Out of 549 cases examined, 263(47.9%) were mycologically proven cases of onychomycosis (139 finger, 124 toe nails), among those 33(6.09%) were only positive in direct microscopic examination. From an etiological point of view, 21.85% of nail infections were caused by yeasts, 10.55% were infected by dermatophytes and 15.5% by non-dermatopyte moulds. *Candida albicans* was the common yeast causative agent (16.73%) followed by *A. flavus* (11.78%), *T. mentagrophytes* (10.26%), *C. parapilosis* (9.12%), *C. tropicalis* (8.74%), *A. fumigatus* (6.08%), *T. rubrum* (4.94%), *A. niger* (3.04%), *Penicillium* spp. (2.66%), *Aspergillus* spp (1.90%), each of *Rhizopus* spp and *Cladosporium* spp (1.52%), *C. guilliermondii* (1.14%), *Scopolariopsis* spp. (1.14%), each of *C. famata*, *C. glabrata*, *C. krusei*, *S. lusitania*, *Acremonium* spp. (0.76%) and *C. homicola* (0.38%), *T. rubrum* (4.94%). *Candida* species were most common responsible agent for onychomycosis in female hands (74.1%) followed by 17.26% non-dermatophyte moulds. Dermatophytes caused tinea unguim of hand (8.63%) and peduum (37.1%) in males. Onychomycosis of finger nails was most prevalent in females while toenail infection was common in male patients.

Conclusion: The yeasts of the Genus *Candida* and non-dermatophyte moulds are dominant cause of female finger nail onychomycosis and dermathophytes are principal cause of both finger and toe nails in males in Tehran.

Keywords: *Onychomycosis, Yeasts, Dermatophytes, Non-dermatophyte moulds, Iran*

Introduction

Onychomycosis is an infection of the nail caused by fungi. Three groups of pathogens are involved: dermatphytes, yeasts and moulds. The later two groups are usually secondary invaders, while the dermatophytes can cause primary infections (1). Onychomycosis is accounted for about 50% of nail disorders. Approximately 30% of patients with a cutaneous fungal infection have concomitant fungal nail disease (2, 3) and a study suggested a prevalence of 18.5% (4) with the number of persons affected apparently on the rise (5). Considerable difference has been shown in prevalence of onychomycosis in various geographical areas. Dermatophytes are evolving as major causative pathogens in countries such as Pakistan (6, 7). India (8), Malaysia (9) Korea(10), Canada (11), United Kingdom (12), USA (13) and Turkey (14) but the yeasts are most frequently reported in Israel (15), Spain (16), Italy (17), Iran (18-20), Saudi Arabia (21), United Arab Emirates (22). Saprophytic mould is also reported as causative agents of infection in Australia (23), Italy (24), UK (3, 25) and Iran (19, 20), India (26) particularly in toenails. The sex-dependency of onychomycosis is still a mater of discussion (27). The disease can occur at any age, but it is more common after puberty (2, 6). Candida species are still largely considered to cause mainly onychomycosis secondary to paronychia disease and onycolysis or associated with peripheral vascular disease (25).

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The mycological study and the identification of etiological agents of onychomycosis are needed to confirm the clinical diagnosis and for the choice of therapy (28). Although there is no need to perform antifungal susceptibility tests for every fungal isolate that causes disease, there are instances, when these tests are warranted and may be extremely useful particularly among patients with disease that is refractory to conventional therapy, as well as patients with unusual isolates. Thus, the aim of this study was to 1) determine the incidence of onychomycosis, 2) identify organisms recovered from the infected nails.

Materials and Methods

Study population

A total 549 of patients clinically suspected of onychomycosis during a one-year period from 2004 to 2005 were studied. Two hundred and fifty seven cases were fingernails with male (M) to female (F) ratio of 82: 175 and 292 cases were toenails with M: F ratio of 108:184. The patients were ranging in age from 15 months to 83 yr. All participants or their guardians gave written consent.

Mycological examination

Diagnosis of onychomycosis was made based on direct microscopy examination (DME) and culture (C) in addition to clinical findings. The nails were swabbed liberally with alcohol before obtaining the specimen according to eliminate bacteria that can interfere with growth of fungi. Nail clipping or subungual scraping were collected from deepest part of the nail and as close as possible to the healthy nail. Then a part of each specimen was mounted in 20% potassium hydroxide (KOH) solution and examined microscopically for the presence of fungal elements (hypha, arthrospores, yeast cells and pseudohyphae). The remainder of each specimen was inoculated onto agar slants of sabouraud's glucose agar (SGA, E. Merck, Germany) with chloramphenicol (0.005%) and with or without cyclohoximide (0.04%), and incubated at 28 ^{o}C for 1-4 wk. The cultures were checked twice weekly for evidence of growth. No growth at the 4th wk was considered as a negative culture. Yeast isolates, if any were then subcultued on SGA in Petri dishes. These isolates were later identified by use of standard laboratory methods, including the germ-tube test, morphology on corn-meal agar- tween 80 (CM-T80) using the dalmau method, CHRO Magar Candida (Microbiology company, France) and API C20 Aux system (Bio Merieux, Marcy, 1 Etoile France).

Each yeast represented a unique isolate from a patient otherwise stated and was maintained as water suspension at room temperature in our laboratory for further use.

Dermatophyte and mould isolates, if any were then subcultured on SGA and potato dextrose agar (PDA) in Petri dished. The species were identified by colony morphology and microscopic examination with lactophenol cotton blue preparation. Differential methods as hair perforation test, *Trichophyton* nutritional media, urease test, Czapek's agar or other selective media were performed for identification of some species whenever needed.

Statistical analysis

Chi-square test of independence and fisher test were used for analysis. Mac nemar test was used for compression of two match samples.

Results

In the study period, 549 patients (359 females, 190 males) suspected of onychomycosis were examined. Patient's age ranging in from 1 to 83 yr with a mean age 39.32±15.6. The commonest affected age group was 31-50 yr followed by 21-30 and 51-60 yr respectively. A total of 263 (47.9%) cases were diagnosed as onychomycosis by mycologic examination. 174 (66.16%) were females and 89(33.84) were males. Among these 263 positive cases, 139 (52.85%) were with fingernail and 124(47.15%) were with toenail onychomycosis. Direct and culture positive findings (*Candida* species, dermatophytes and non-dermatophyte moulds) were observed in 230(41.9%) and direct positive finding observed in only 33 (6.01%) of cases (Table 1).

The Mac nermar test showed significant difference between these two direct and culture methods in detecting the etiologic agent of infected nails with superiority of direct examination (X^2= 33, P<0.001). However statistical analysis revealed no significant differences between frequency of affected male and female patients (X^2= 0.12, P= 0.72, Odds ratio (OR)= 1.07 and Confidence interval (CI)= 0.74-1.54), but there was a relation between sex and type of causal agents (X^2= 34.44, P< 0.001, df= 3) (Table 2).

Candida albicans was the major *Candida* species (16.73%) followed by *C. parapsilosis* (9.12%) and *C. tropicalis* (8.74%) of all 21.85% *Candida* spp. Among dermatophyte species *Trichophyton mentagrophytes* was almost twice as often as *T. rubrum*. *Aspergillus flavus* (11.78%) was the most commonest species of all non-dermatophytic moulds followed by *A. funigatus* (6.08%), *A. niger* (3.04%) and *penicillium* spp. (2.66%), (Table 3).

According to sex and *Candida* spp. as etiologic, agents, significant difference was observed (X^2=7, P< 0.01, OR=1.88, CI=1.15-3.11) and infection was 2-fold more common in females than males (Table 2).

In patients with dermatophytic onychomycosis, also significant difference was observed (X^2= 7.38, P< 0.001, OR= 0.24, CI=0.13-0.43) by means that infection is predominant among males (Table 2). On the other hand no difference was found in the distribution of causal non-dermatophytic moulds between males and females (X^2= 1.2, P= 0.27, OR= 1.32, CI= 0.78-2.26) (Table 2).

The organisms causing fingernail onychomycosis were 74.1% *Candida* spp, 8.63% dermatophytes, 17.26% non-dermatophyte moulds. The corresponding organisms causing toenail onychomycosis were 13.7%, 37.1% and 17.26% respectively (Table 3).

In present study most of fingernail onychomycosis was seen in females than males (X^2= 12.01, P< 0.001, OR= 0.46, CI= 0.29-0.73) and toenail infection was significantly common in males than females (X^2=10.48, P< 0. 01, OR= 1.95, CI= 1.27-2.99), when the whole number of patients was taken into account (Table 3).

The Table 4 presents the relation between sex and fingernail infection with regard to causative organisms (X^2= 27.4, P< 0.001). When *Candida* species and dermatophytes as etiologic agents of fingernail and toenail infection were compared, significant difference was observed between sex and fingernail infection (P= 0.002) and also between sex and toenail onychomycosis (X^2=8.68, P= 0.003) (Table 4). Moreover while *Candida* species and non-dermatophytes as causative agents and location of infection were compared, significant difference was observed between sex and fingernail infection (P= 0.036) but no significant difference between sex and toenail onychomycosis was observed (X^2= 1.45, P= 0.22) (Table 4).

Furthermore, when dermatophytes and non-dermatophytes as etiologic agents of finger and toenails were compared, difference was significant between sex and toenail infection (X^2= 7.02, P= 0.008) (Table 4).

Table 1: Mycological examination in onychomycosis

Direct examination	Culture				Total	
	Positive		Negative			
	n	%	n	%	n	%
Positive	230	41.9	33	6.01 52.1	263	47.9
Negative	0.0	0.0	286		286	52.1
Total	230	41.9	319	58.1	549	100

Table 2: Frequency distribution of onychomycosis according to gender

Onychomycosis	Gender				Total	
	Female		Male			
	n	%	n	%	n	%
Yeasts	94	26.18	26	13.68	120	21.85
Dermatophytes	20	5.57	38	20	58	10.55
Moulds	60	16.72	25	13.16	85	15.5
Negative	185	51.53	101	53.16	286	52.1
Total	359	65.4	190	34.6	549	100

No= Number

Table 3: Fungal isolates from infected nails according to gender and location

Fungal pathogens	Fingernail		Toenail		n (%)
	Male	Female	Male	Female	
Yeasts					
Candida albicans	6	35	0	3	44(16.73)
Candida parapsilosis	3	16	0	5	24(9.12)
Candida tropicalis	4	18	0	1	23(8.74)
Candida guilliermondii	0	1	2	0	3 (1.14)
Candida famata	1	1	0	0	2(0.76)
Candida glabrata	0	0	1	1	2(0.76)
Candida krusei	0	2	0	0	2(0.76)
Candida lusitaniae	2	0	0	0	2(0.76)
Candida homicola	0	0	0	1	1(0.38)
Total	16	73	3	11	103(39.16)
Dermatophytes					
Trichophyton mentagrophytes	4	0	15	8	27(10.26)
Trichophyton rubrum	4	0	5	4	13(4.94)
Unidentified	0	2	3	0	5(1.90)
Total	8	2	23	12	45(17.11)
Moulds					
Aspergillus flavus	0	7	6	18	31(11.78)
Aspergillus fumigatus	0	8	0	8	16(6.08)
Aspergillus niger	0	2	5	1	8(3.04)
Aspergillus spp.	0	0	3	2	5(1.90)
Penicillium spp.	0	2	4	1	7(2.66)
Rhizopus spp.	0	2	0	2	4(1.52)
Cladosporium spp.	0	1	3	0	4(1.52)
Scopolariopsis spp.	1	0	0	2	3(1.14)
Acremonium spp.	0	0	2	0	2(0.76)
Unidentified	0	0	0	2	2(0.76)
Total	1	22	23	36	82(31.18)
D + C –	6	11	9	7	33((12.55)
Total	31	108	58	66	263(100)

Abbreviations: D=Direct microscopic examination, C = Culture, += Positive, - = Negative

Table 4: Frequency distribution of fungal pathogens from nails according to gender and location

Fungal pathogens	Fingernails				Toenails			
	Female		Male		Female		Male	
	n	%	n	%	n	%	n	%
Yeasts	81	46.28	22	26.83	13	7.06	4	3.70
Dermatophytes	4	2.29	8	9.76	16	8.69	30	27.77
Moulds	23	13.14	1	1.22	37	20.11	24	22.22
Negative	67	38.28	51	62.19	118	64.13	50	46.3
Total	175	100	82	100	184	100	108	100

Discussion

A routinely used rapid test for the diagnosis onychomycosis in the mycology laboratory is the DME of KOH preparation. The difficulty of isolating fungi from microscopically positive nails and low correlation of DME and culture findings are well known as observed in our study (Table 1), (1, 6, 9, 29).

As the treatment of onychomycosis generally requires long-term therapy with an oral antifungal, it is essential to diagnose the infection accurately. An inaccurate negative diagnosis will lead to prolonged nail disfigurement and discomfort the patient, whereas an inaccurate positive diagnosis may lead to long-term, useless and expressive treatment regime. Clinicians and laboratory staff alike often have a misconception that the diagnosis of onychomycosis is simple in theory it should be-but in practice, it is often difficult (17). From 549 patients with clinically suspected of fungal nail infection, only 47.9% confirmed to be infected on mycological examination. With regardless to causative agents, there was no notable sex difference between the frequencies of nail-infected patients when the whole number of patients was taken into account. This finding was in agreement with some reports (12, 30) but distinct from others (12, 31, 32). Fungal infection of fingernail and toenail accounted for 54.3% and 42.32% respectively. The commonest age group affected by *Candida* species was 41-50 yr followed by 31-40 and 21-30 yr. While dermatphytes affected mostly age group of 61-70 yr, but non-dermatophyte moulds affected commonly age group of 41-50 followed by 21-30 yr. There was only one child (1 yr old) in the present study, this highlights that the disease is unusual prior to puberty (6).

One previous report has indicated that dermatophytes are dominant cause of onychomycosis in Tehran (33) but the findings of this survey similar to the reports from Tehran as well as other investigators from Iran (19, 20, 34, 36) and different part of world (16, 21, 29, 37-40) indicate that Genus of *Candida* with 21.85% of all cases are the principal etiological agents of onychomycosis particularly in females.

C. albicans was the most frequent isolated species of Genus *Candida* followed by *C. parpsilosis* and *C. tropicalis*. This finding confirms early reports from Tehran and other parts of Iran that found the similar results (18, 19, 36, 41).

In contrast to other reports that mentioned the dermatophytes were the most common agents of onychomycosis (2, 8, 9, 13, 14, 28, 33-36, 38-44), in the present study onychomycosis due to dermatophytes was accounted for 10.55% of all fungal nail infections (Table 2) and it was common among males than females. According to the frequencies, the anthropophilic *T. mentagrophytes* and *T. rubrum* were responsible for most cases of dermatophyte-induced onychomycosis in both fingernails and toenails respectively. Although this findings are in accordance with other reports (33, 34, 36) from Iran and from Rome (37), Pakistan (39), Canada (45), Nepal (46) and Singapor (30), but it is in contrary to another reports (19), and also Khosravi (42) from Tehran as well as from UK (12), Malysia (9) and India (8), in which *T. rubrum* was the most frequently isolated dermatophyte followed by either *T. mentagrophytes*, *T.*

violaceum and *E. floccosum*. Although Ardehalis' study in the 1973 (47) showed that, the most common agents of onychomycosis in Iran were *T. schoenlienii* and *T. violaceum* respectively, but it is quit obvious from several 1980 afterwards studies that, these species were replaced by *T. mentagrophytes* and *T. rubrum* (19, 20) with an exception of the study of 187 patients in 2000 from Iran, which indicated that *T. mentagrophytes* and *T. violaceum* being increased whereas *T. rubrum* decreased (33) during that period of study. We have adopted the criteria of repeated isolation (at least three times) of the same mould in addition to positive microscopy to establish it as a pathogen. In this manner, non-dermatophyte mould nail infections accounted for 15.5% of all onychomycosis in present study with apparently females more affected than males, but this difference was not statistically significant. Similar to previous studies from Iran (19, 34, 36) and from Nepal (46) the predominant moulds were *Aspergillus* spp. (*A. flavus, A. fumigatus, A. niger*), *penicillium* spp. and *Rhizopus* spp. respectively. In other reports from Spain (48), Australia (23), India (26) and Iran (33) the most common non-dermatophytes was *Scopolariopsis* followed either by *Aspergillus* spp. or other moulds as *Alternaria* spp., *Fusarium* spp. (49).

An interesting outcome of this study is that, cases of non-dermatophyte mould nail infection has increased in frequency during last two decades when compared with other reports (19, 20, 34). Moreover, our findings showed frequency of nondermatophytic mould onychomycosis is also higher than dermatophytic onychomycosis.

Our survey similar to other studies (18, 19, 22, 34) showed that fingernail onychomycosis due to Candida species is significantly high in females than males (X^2= 8.8, P= 0.003, OR= 2.35, CI= 1.28-4.34), but no significant difference was observed between female and male toenail Candida onychomycosis (OR=1.98). This finding is in contrary to Gerame-Shoar et al. study (34) in which they found high rate of females toenail infection rather than fingernail involvement.

While in the present study non-dermatophyte mould fingernail infection is significantly high in females than males (X^2= 9.38, P= o.003, OR= 12.26, CI= 1.71-248.17), but no difference was found between two sexes toenail onychomycosis due to above-mentioned fungi (OR= 0.88). This finding is in contrast to Gerami-Shoar et al. study (34) in which they found high rate of females toenail mould infection rather than fingernail involvement, and also to other study (36) in which they reported no preference in site and sex when the cases affected by non-dermatophyte moulds.

According to the history of the studied patients the increase in fingernail involvement was due to increased incidence of occupation relate trauma, frequent immersion of hands in water or exposure to chemicals.

Dermatophytic onychomycosis of both fingernails and toenails were more common in males than females. (P= 0.006, OR= 0.19, CI= 0.05-0.72 and X^2= 18.67, P< 0.001, OR= 0.25, CI= 0.12-.5 respectively). Although these findings are in agreement with some reports (19, 31) but are in contrary to Gerami-Shoar et al. (34) in which they pointed out the rate of affected toenails by dermatophytes were almost equal in both sexes.

In conclusion, this study has demonstrated that yeasts of the Genus Candida and nondermatophyte moulds are the dominant cause of women fingernail onychomycosis in Tehran, but that dermatophytes are principal cause of finger and toe nail infection in men.

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The authors declare that there is no conflict of interests.

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