A. M. Magomedova et al /J. Pharm. Sci. & Res. Vol. 10(9), 2018, 2276-2278

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Candidal Infection of Mucous Membranes and Nail Plates

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Abstract

Despite the evolution of modern diagnostic methods of molecular biology in determining the resistance of yeast-like fungi to antimycotic drugs, the use of these methods in everyday diagnostic practice is limited and is not always the only way to achieve a valuable clinical effect. The aim of the study was to analyze risk factors for therapy resistance in patients with candidal infection of mucous membranes and nail plates. The authors conducted a cross-sectional study of 1,896 outpatient subjects by using clinical/laboratory and statistical methods with an average age of 34±4.8 years. In order to study the quantitative contribution of each individual risk factor to the development of therapy resistance, we applied the logistic regression procedure with the calculation of odds ratio and its 95% confidence interval. Critical level of significance of differences in groups was established on type I error boundary presented as $\alpha<0.05$. Statistical analysis was performed by using SPSS 20 for Windows. C. albicans predominated in etiological structure of candidal infection of mucous membranes and nail plates - 88.13%. Patients were more likely to develop therapy resistance in the presence of such risk factors as smoking – by 2.07 times (95% CI 1.43, 2.56), alcohol intake – by 3.82 times (95% CI 2.99; 4.00), noncompliance with drug regimen – by 4.71 times (95% CI 3.97, 4.85), prior self-medication – by 3.21 times (95% CI 1.15, 3.57), lack of microbiological examination on the pathogen sensitivity – by 1.84 times (95% 1.36, 2.18), concomitant somatic pathology – by 1.53 times (95% 1.23, 1.88), intake of immunosuppressants – by 2.11 times (95% CI 1.47, 2.35), and intake of hormones – by 1.9 times (95% CI 1.42, 2.13). Lesions of the mucous membranes and nail plates can become chronic, recurrent and therapy resistant when ignoring many common risk factors, both medical and personal ones. An integrated approach with an adequate microbiological diagnosis and determining the sensitivity of the pathogen prior to treatment as well as eliminating risk factors in the population can become a prerequisite for effective management of patients with candidiasis.

Keywords: candidal onychomycosis, candidiasis of nail plates, candidiasis of the mucous membranes, risk factor; therapy resistance.

INTRODUCTION

Opportunistic yeast-like fungi of the Candida genus belonging to the family Criptococcaceae are known as etiological agents of candidiasis. According to the morphological structure, these fungi are deuteromycetes representing an independent genus of about 150 species [1]. The largest proportion among the fungi of this genus belongs to Candida albicans. Its proportion is equal up to 90-93% according to various sources. However, more recently, we have been able to see such pathogenic species as Candida tropicalis (5%), Candida krusei (10.6%), Candida Stellatoidea, Candida glabrata, Candida lusitaniae, Candida Rugosa (about 3%), and Candida parapsiliosis (about 3%) [2].

According to some studies, every second person in the world has suffered from any form of candidal infection at least once. In the United States of America, candidal infection ranks fourth after staphylococcal group (S. aureus and S. epidermidis) and enterococci. It should be noted that the infection caused by the fungi of Candida genus takes a leading place in the etiologic structure of pathogens and takes the first place for mortality reasons from nosocomial septic conditions. Morphologically, Candida is a unicellular aerobic microorganism, relatively small, round shape. And it is referred to facultative pathogens. Along with this, a typical feature of fungi of this genus is the ability to form pseudomycelia, blastopores located on the constrictions of pseudomycelia, and chlamydospores, which are spores with a dense double shell. At the same time, fungi of the genus Candida spp. can be the reason of a mixed infection with other fungi, bacteria, viruses, etc. [3].

Candidal infection of mucous membranes according to the classification of N.D. Sheklakov belongs to the group of superficial candidiasis of mucous membranes, skin, nails [4].

Onychomycosis, a fungal nail infection, is a common medical problem that affects predominately adult people. Some authors report that about 20% of those aged from 40 to 60 years have or had an episode of onychomycosis [5-7].

Frequent exposure to fungal infections, irrational use of antibiotics, HIV infection and immunosuppressive drug therapy are predisposing factors for the onset of onychomycosis [8]. Other factors contributing to the development of the disease include diabetes mellitus, peripheral vascular disease, chronic smoking and nail trauma. It is important to note that one in five HIV patients has fungal infections associated with nail plate lesions [9]. Moreover, onychomycosis is currently considered to be one of the marker signs of HIV infection [10, 11].

Mainly, three species of fungi are involved in the development of onychomycosis: dermatophytes, Candida species and nondermatophyte forms. It is known that Candida species inhabiting skin and mucous membranes of humans as conditionally pathogenic flora stimulate the development of opportunistic infections from less serious surface lesions to dangerous systemic diseases in conditions when the host's immunity is significantly suppressed by external factors. Superficial candidiasis is the most common form of Candida-related infections, can include one or more than one tissues, including skin, mucous membranes, nails and hair, whereas candidal infection limited to nails and toes is more known as candidal onychomycosis [12]. According to some reports, there are suggestions that Candida species are the main cause of all forms of onychomycosis [5, 6, 12].

Thus, taking into account high prevalence of the disease, a number of epidemiological issues which are open to discussion, risk factors and the effectiveness of therapy, we can say that the subject of candidal infection of the mucous and nail plates is highly relevant in this field of knowledge.

The aim of this study was to analyze risk factors for therapy resistance in patients with candidal infection of mucous membranes and nail plates.

MATERIALS AND METHODS

Methods

To confirm the etiology of the disease in the study group, we conducted a microscopic study of the direct smear from the mucous membranes, as well as culture diagnostics of scrapings from the affected areas of the mucous and nail plates with determination of sensitivity to antifungal drugs on the Fungi test micropanel (USA). An enzyme immunoassay test for the detection of specific IgG antibodies against the fungi of Candida genus was conducted with the use of the diagnostic kits of the company Vector-Best (Russia) on an Alfa Prime analyzer made by Meredith Diagnostics (England).

Therapy for candidiasis of the mucous membranes was carried out in accordance with the recommendations of the Infectious Diseases Society of America [2]. The following drugs were prescribed to patients: clotrimazole (topically 1 tablet 5

times a day) or nystatin suspension (100,000 U/mL); fluconazole per os (100 mg per day for 7-14 days).

Therapy for candidiasis of the nail plates was also performed in accordance with recommendations of the Infectious Diseases Society of America [2]. Itraconazole (200 mg twice a day for 1 week, then monthly for 3-4 months) was recommended to the patients.

Therapy resistance was determined in the absence of clinical and laboratory effects in more than 14 days of the treatment in case of mucosal candidiasis, and more than 4 months of therapy in case of candidal onychomycosis.

Patients

We conducted a one-stage cross-sectional study of risk factors for therapy resistance in patients with candidal infection of mucous membranes and nail plates on the basis of the Republican Dermatovenerologic Dispensary in the city of Makhachkala in the period from April 2016 to January 2018. The total number of participants was 1,896 people of both sexes with an average age of 34±4.8 years. The majority of the participants in the study were represented by females, the number of which was 75.16% (1,425 out of 1,896). The majority of patients belonged to urban residents (82.96%), while a lower number of the patients belonged to rural (17.04%) residents. In this case, among all patients, the majority were employed - 77.22% (Table 1).

Table 1. Basic characteristics of the study participants (n=1,896)

Characteristic	n	%
Age (Mean ± standard deviation)	34±4.8 years	
Sex		
Male	471	24.84
Female	1,425	75.16
Place of residence		
City	1,573	82.96
Rural	323	17.04
Employment		
Unemployed	432	22.78
Employed	1,464	77.22

Adherence to ethical norms (ethics).

Before enrollment in the study, all the participants signed an informed consent form. Each of the group of participants received guarantees of complete anonymity and confidentiality of personal data. The study was approved by the local ethical commission of the Federal State Budgetary Educational Institution of Higher Education "Dagestan State Medical University" of the Ministry of Health of Russia, Makhachkala.

Statistical analysis

The results of the study were subjected to mathematical analysis by using the methods of descriptive statistics. For categorical variables, the data were given in the form of absolute numbers and their percentage expression. For quantitative data, we provided measurement of the main trends with description of dispersion in form of the standard deviation from the mean value.

In order to determine the quantitative contribution of each risk factor to the development of therapy resistance, we used a logistic regression with calculation of the odds ratio and its 95% confidence interval (95% CI). The critical level of significance of differences in groups was established on type I error boundary presented as $\alpha<0.05$. Statistical analysis procedure was performed by using SPSS 20 for Windows.

RESULTS

In the etiologic structure of the causative agents, C. albicans predominated - 88.13%, C. parapsilosis were 2.74%, C. glabrata - 2.48%, C. krusei - 1.11%, and C. lusitaniae - 5.54% (Figure 1).

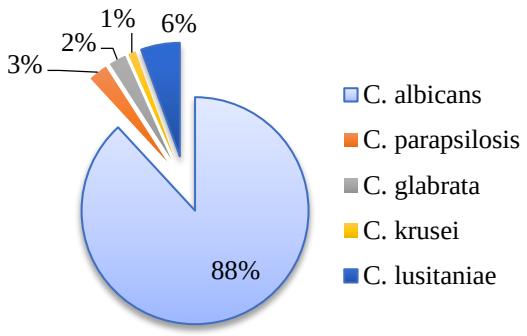

Figure 1. Etiological profile in the study group (n = 1,896)

When analyzing the patient's medical history, we have found that smoking was common in 44.36%, alcohol intake during previous antifungal therapy – in 23.15%, failure to adhere to the drug regimen – in 29.69%, and previous self-medication prescribed by pharmacists in pharmacy or due to the experience of people from the environment – in 83.18% (Table 2).

Table 2. Personal risk factors for therapy resistance (n = 1,896)

Risk Factor	n	%
Smoking	841	44.36
Alcohol consumption	439	23.15
Noncompliance with drug regimen	563	29.69
Previous self-treatment	1577	83.18

When analyzing the anamnestic data, we have found out that in almost every third patient there was no microbiological examination for sensitivity to antimycotics - 38.77%. More than 20% of individuals suffered from immunocompromising concomitant pathology, such as diabetes mellitus (DM), bronchial asthma and psoriasis. An intake of immunosuppressants and hormones was observed in 0.58% and 5.49% of patients, respectively (Table 3).

Table 3. Medical risk factors for therapy resistance (n = 1,896)

Risk Factor	n	%
Lack of microbial sensitivity test	735	38.77
Concomitant somatic pathology (diabetes, asthma, psoriasis)	462	24.37
Intake of immunosuppressants	11	0.58
Administration of hormones	104	5.49

After assessing the prevalence of risk factors and identifying individuals with therapy resistance, we conducted a logistic regression procedure, during which the complex contribution of each of the risk factors was evaluated with the correction for the influence of other factors. We have found that various risk factors increased therapy resistance in the following way: smoking - 2.07 times (95% CI 1.43, 2.56), alcohol intake - 3.82 times (95% CI 2.99 4.00), noncompliance with the regimen - 4.71 times (95% CI 3.97, 4.85), prior self-medication - 3.21 times (95% CI 1.15, 3.57), lack of microbial studies on the sensitivity of the causative agent - 1.84 times (95% CI, 1.36, 2.18), concomitant somatic pathology - 1.53 times (95% CI 1.23, 1.88), immunosuppressant intake - 2.11 times (95% CI 1.47, 2.35), and hormone intake - 1.9 times (95% CI 1.42, 2.13) (Table 4).

Table 4. Complex contribution of risk factors to the development of therapy resistance

	Odds ratio	Lower 95% CI	Upper 95% CI
Personal factors			
Smoking	2.07	1.43	2.56
Alcohol consumption	3.82	2.99	4.00
Noncompliance with drug regimen	4.71	3.97	4.85
Previous self-treatment	3.21	1.15	3.57
Medical factors			
Absence of microbiological examination for sensitivity to AF	1.84	1.36	2.18
Concomitant somatic pathology (diabetes, asthma, psoriasis)	1.53	1.23	1.88
Intake of immunosuppressants	2.11	1.47	2.35
Intake of hormones	1.9	1.42	2.13

DISCUSSION

Despite the fact that the patients with candidiasis are predisposed to other chronic fungal infections and acute viral and bacterial infections, the most persistent morphological lesions usually occur due to Candida species. The presence of a well tolerated oral preparation with good clinical activity against Candida infection will represent a significant advance in the therapy of these patients. However, the fight against factors of therapy resistance cannot be excluded from the general strategy of anti-Candida therapy [13].

Often, onychomycosis cannot be treated by traditional methods of treatment. According to some reports, onychomycosis is the most difficult for therapy from all superficial fungal infections [14]. Chronic nature of candidal onychomycosis with a high tendency to relapse is often explained by the difficulty in pathogen elimination. However, onychomycosis should be treated quickly in case of immunocompromised state, such as diabetes mellitus, senior age and HIV infection. Otherwise systemic dissemination can occur [14].

First of all, it is important to get rid of a predisposing risk factor and maximize the patient's immunity to therapy in order to see the maximum effect of antifungal treatment. Antifungal drugs play an important role in eliminating Candida from the nail plate. However, clinical data only do not indicate an antifungal therapy for onychomycosis. When choosing a suitable antifungal agent, several other factors need to be considered, such as general health of the patient, antifungal sensitivity of the microorganism, degree of fungi infestation, and patient compliance with drug regimen [15].

Slow growth rate of nails, hardness of the nail plate and location of the infectious process between nail bed and nail plate are the main factors that prevent elimination of fungal elements during the treatment. Patient's adherence is also a determining factor in success of the treatment. However, it becomes impossible when patients do not seek treatment in clinics when the disease has minimal manifestations, or they are embarrassed to consult a doctor for any reason [16].

Proper collection of patient anamnesis and medical history as well as proper clinical examination, accompanied by microbiological and histopathological study, are the keys for effective treatment of candidiasis of mucous membranes and nail plates. In addition, improving patient awareness of reducing personal risk factors, nail hygiene and appropriate treatment procedures also help in the treatment of patients.

CONCLUSIONS

The importance of treating candidiasis of mucous membranes and nail plates is often underestimated both by patients and by physicians. Lesions of mucous membranes can take chronic and recurrent character, become therapy resistant while ignoring many common risk factors, both medical and personal ones. An infected nail is a chronic infection reservoir, which can cause repeated mycotic infections of the skin and mucous membranes. Candida species have become important pathogens that cause onychomycosis in immunocompromised populations with a wide spread of personal and medical risk factors and altered fungal virulence. This scientific area requires additional in-depth studies.

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