New horizons in the integrative therapy of Onychomycosis

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In recent years we are witnessing an ever wider use of new technologies in various fields of medicine. The idea of proposing new therapeutic approaches, less invasive and with fewer side effects becomes the mission of many hi-tech companies. Fields of clinical application widen more and more, and a growing list of diseases and clinical conditions find therapeutic solutions by using new technologies, abandoning traditional and obsolete therapeutic methods. One of the fields that deserved the attention of several companies that manufacture lasers and intense pulsed light technologies, seems to be podiatry in the treatment of Onychomycosis.

Introduction

Onychomycosis is one of the commonest dermatological conditions. It is a chronic infection of the nail apparatus, which frequently leads to its deformity. The term Onychomycosis refers to all the fungal infections of the nail rather they incurred by *Dermatophytes*, yeasts or molds. The fungal infection usually does not involve the nails evenly or symmetrically but affects only one or two nails primarily or secondarily to other nails disease. The majority of infections caused by filamentous fungi called *Dermatophytes*. Yeasts of the genus Candida, in particular *Candida Albicans*, are the second most common cause of nails infection. Rarely some other fungi can also affect the nails, such as *Scopulariopsis*, *Hendersonula* and *Scytalidiume*. Although these infections appear to be very rare, it is important to identify correctly the causative agent, since most cases respond poorly or not at all to the antifungal treatments currently available. Onychomycosis is generally a disease of the adult; toenails and especially the big toe are more commonly affected than the hands. Environmental factors are certainly important in the epidemiology of Onychomycosis that, in fact, seems to be much rarer among populations that do not wear shoes, while it is more frequent in civilized countries, especially in those categories of people who fit athletic shoes that avoid adequate ventilation. Attending

gyms and swimming pools, changing rooms and public toilets, involve a major risk factor; considered the promiscuity of people and the warm and moist environment. Often it originates from pre-existing skin outbreaks; in fact, can often be caused by fungal infection between the toes or by contiguity or indirectly through shoes and socks, which get in contact with the nail. Therefore, it is possible to have a contagion indirectly through contaminated objects or clothing. This is the most common mode of transmission of *Dermatophyte* Onychomycosis. Moreover, the infection can occur by:

- Autoinoculation even at a distance through scratching as in the case of *Candida albicans*, responsible for Onychomycosis more frequently in females, because of *Candida perionyxis*. This disease affects mostly housewives, as they are subjected to a prolonged contact with water and rubber gloves.
- Eteroinoculation which can be direct (contact of the fungal infection lamina of the mother with the one of the child) or indirect (cutting the nail with non-sterile instruments) Other predisposal factors to fungal infection can also be considered the indiscriminate use of drugs, detergents or irritating substances, which lower the immune system. The host immune defense has a very important role in the establishment of the infection. This explains why the incidence of fungal infection in immune compromised patients increases significantly.

Onychomycosis is not merely a cosmetic problem; it interferes with lifestyle and occupation, it causes physical pain, it creates psychological stress and compromise quality of life to a certain extent. (Drake LA et al. J Am Acad Dermatol. 1998: 38; 702 - 704)

Classification (D.T. Roberts, W.D. Taylor and J. Boyle 2003)

1. Distal and Lateral Subungual Onychomycosis (DLSO)

- DLSO accounts for the majority of cases, almost always due to *Dermatophyte* infection. *(Trichophyton Rubrum)*
- It affects the hyponychium at the lateral edges initially.
- Spreads proximally along the nail bed resulting in subungual hyperkeratosis Onycholysis.

2. Superficial White Onychomycosis (SWO)

- SWO is almost always due to Dermatophyte infection, most commonly *Trichophyton Mentagrophytes*.
- Much less common than DLSO.
- Affects the surface of the nail plate rather the nail bed.
- White discoloration and surface of the nail plate is noticeably flaky.

3. Proximal Subungual Onychomycosis (PSO)

- Uncommon variety of *Dermatophyte* infection related to intercurrent disease.
- Immunosuppressed patients may present with this variety of *Dermatophyte* infection
- Peripheral vascular disease and diabetes.
- Evidence of intercurrent disease should therefore be considered in patients with PSO.

4. Candidal Onychomycosis

I. Chronic paronychia with secondary nail dystrophy (wet occupations)
II. Distal nail infection (Raynaud's phenomenon or vascular insufficiency)
III. Chronic mucocutaneous Candidiasis (immunosuppressed)
IV. Secondary Candidiasis (e.g. psoriasis)

5. Total dystrophic Onychomycosis

   Any of the above varieties of Onychomycosis may eventually progress to total nail dystrophy where the nail plate is almost completely destroyed.

Diagnosis criteria

During the diagnosis process of Onychomycosis, it is important to bear in mind the clinical picture of nail infections, though it is impossible to make a definitive diagnosis based only on clinical examination. It is therefore of essential importance, the confirmation of the laboratory, both for an accurate diagnosis and for monitoring the treatment. Laboratory diagnosis of fungal infections is based on microscopic examination of the clinical material in a

10% solution of KOH (potassium hydroxide) and on the mycological culture. The reliability of these procedures is given by the professionalism of the laboratory staff and the quality of the sample examined, in addition, the patient should not have applied topical antifungal for at least 2 weeks before the test.

Interpretation of results:

Recognition of fungal elements in a sample of fingernail requires considerable experience, that's why, it is important to contact a specialized laboratory. In fact, some of the fungal elements can be not detected by inexperienced eyes and thus give rise to a false negative. On the contrary, cell walls, fibers or other artifacts can be exchanged with the fungus and result in false positives. The direct visualization under a microscope of fungal elements does not identify the type of fungus, with the exception of the recognition of yeasts rather than *Dermatophytes*. Positive identification can only be made through fungal culture. Yeasts grow within 3 days, while most of the Dermatophytes grow very slowly in culture, so as to be hardly identified before 7 - 10 days and the culture also should be continued for at least 3 weeks prior to define negative result. A new diagnostic method is gaining ground nowadays, based on a molecular approach which greatly facilitates the obtaining of the final diagnosis, drastically shortening the waiting time and increasing the accuracy to a negligible margin of error. The mechanism is a polymerase chain reaction (PCR) based multiplex application. From DNA isolation to diagnosis the new device exceeds traditional procedures by performing highest quality identification of *Dermatophytes i*n less than one day, consequently, providing up to 4 weeks gain in time. The multiplex PCR application eliminates the eventuality of miss interpretation caused by the dominance of a particular species or an increased contamination risk of culture plates over the long analysis time. A simultaneous identification and differentiation of 21 *Dermatomycosis* causing pathogens on the molecular level, results in a rapid clarification of disease etiology, enabling a specific therapy selection.

Pharmacological therapy

Both topical and oral agents are available for the treatment of nail fungus infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. This defined as the primary end-point in almost all properly conducted studies. Clinical improvement and clinical cure are secondary end points based on a strict scoring system of clinical abnormalities in the nail apparatus. It must be recognized that successful eradication of the fungus does not always render the nails normal as they may have been dystrophic prior to infection. Such dystrophy may be due to trauma or non fungal nail pathology.

Topical treatment

There are several topical anti-mycotic preparations, commercially available in the forms of lotions, creams, gels, dyes, foams, lacquers, sprays, etc. The choice is very important for treatment success. In most cases topical treatment is the solution of first choice as they spared the risks of side effects and can be easily purchased as OTC. The antifungal drug may be associated with: Corticosteroid in the hyper-reactive forms and Antibiotics for over microbial infection.
Often, they are not sufficiently effective, because their ability to penetrate through the nail plate is limited and the concentrations of the active ingredients are rather weak.
The topical medications most commonly used are: *Miconazole Nitrate, Clotrimazole, Tioconazole, Amorolfine, Ciclopirox, Naftifine,* etc.
Topical antifungal agents often prove disappointing in the treatment of Onychomycosis because they require a long and constant treatment, and reported at a low mycological cure.

Systemic treatment

Griseofulvin: is a substance isolated from *Penicillum Griseofulvum*. It is inactive towards the bacteria, but causes wrinkling and inhibition of fungal hyphae. It was introduced for the treatment of *Dermatophytosis* which affects the skin, hair or nails. It has been a mainstay of systemic treatment of *Dermatophyte* Onychomycosis in the last thirty years. It binds to the keratin making it resistant to the growth of fungi, so the re-growth of hair and nails will be free of infection. The intake can cause nausea, headache, intolerance to alcohol and an annoying photosensitivity in some patients. This therapy has been disappointing for the treatment of Onychomycosis of the foot with only 30% of healing. *Ketoconazole* is active on *Dermatophytes*. Has a limited use due to side effects such as nausea, headaches, digestive disorders, gynecomastia, impotence, and often results toxic to the liver. Triazoles: are azole derivatives of more recent development. They are active on both *Dermatophytes* and *Candida*, the side effects are less severe compared to *Ketoconazole*; the common speeches are Itraconazole and *Fluconazole*. *Allylamines* these compounds have a different mechanism of action from the Azole derivatives; they in fact inhibit squalene epoxidase. This enzyme is necessary for the biosynthesis of the fungal cell membrane. *Terbinafine* is one of the Allyalmine that has yielded good results and high cure rate in the treatment of Onychomycosis of the foot. Treatment times ranging from 3 to 6 months.

Generally, these traditional methods are considered poorly effective (vicious circle expectation- disappointment - expectation) and not always compatible with patients health.

Intense Pulsed Light Therapy

An innovative method of treating Onychomycosis is based on delivering a beam of intense pulsed light (IPL) radiation into a target area, to thermally deactivate pathogens microorganism without causing substantial unwanted injury. According to the Selective Photothermolysis theory, such radiation absorbed by the target tissue is converted to thermal energy that cause deactivation of the parasite organism by destroying it or render it unable to grow or reproduce itself. A polychromatic spectrum of wavelengths (530 nm – 1100 nm) can fairly be advantageous as it allows a wide range of chromophores absorption. Fungal coloration in the affected area tends to assume yellow to brown tones that act as chromophores and therefore absorb a part of the visible light energy (photons), which result in specific thermal damage. The quantity of energy and the consequent temperature, applied to the target (nail bed) must be sufficient (presumably around 45°C) to achieve the fungus deactivation, but too high to cause collateral damage on adjacent tissue. This key factor is contemplated in the so called "Thermal Relaxation Time" (TRT) concept. TRT parameter is used for estimating the time required for heat to conduct away from directly heated tissue region. It represents the time taken for heated tissue to lose ~50% of its heat through diffusion. The epidermis TRT duration is 10 ms; exposure times should not exceed this value. Pulse duration assumes, therefore, together with its wavelength a critical importance in determination of lesion clearance and minimizing side effects. Pulse duration choice is as important as that of the wavelength.

Clinical studies

In a research conducted in the second semester of 2011 by the Italian Institute of Podiatry (IPI) in association with the degree course in podiatry of Rome University "La Sapienza", an innovative IPL device "Fungus Clinic"™ produced by Formatk Systems Ltd. - Israel, has been tested as an alternative therapeutic method for nail fungus (Onychomycosis). This research was subject of a thesis as part of the degree course in podiatry in the academic year 2011-2012. Twenty five patients affected by Onychomycosis attended the study and were treated regularly in this institute. The trials results demonstrated significant cure validity in terms of nail clearance, laboratory analysis and led to the following conclusions:
The Onychomycosis in general and particularly those of Dermatophytes, constitute one of the most common nail diseases. Although not representing a

severe disease, in terms of morbidity and mortality, is often a source of suffering for these patients, which sometimes find hard to accept their nail's alteration or deformation. From the study, emerged important results, claiming the effectiveness of Fungus Clinic IPL device (Formatk Systems Ltd. Israel) in the treatment of Onychomycosis. The culture analysis performed at the end of treatment, carried out in the same laboratory where it was first done, shows that none of the patients treated presented any longer an active Onychomycosis, which demonstrate the validity of the technology.

Another case study was conducted in Israel by Dr. M. Shohat in 2012, using the same technology. Dr. Shohat, a senior dermatologist from Rabin Medical Center, studied the curative effects of "Fungus Clinic" on 10 patients affected by DLSO in his own clinic. The laboratory analysis of all 10 patients, 12 weeks after the final session pointed out the following results: Mycological culture tests have shown a negative result 3 months after the last treatment in 70% of the group. Most of patients demonstrated a significant improvement in the nail morphology (less turbidity) and lesion clearance; visible improvements in the nail plate can be summarized in the following table. A partial and variable neo genesis of the nail matrix and nail plate underneath the lesion area was observed (especially the lunula zone), (as shown in the pictures). Microscopy direct examination found traces of spores / hyphaes in few patients although mycology culture resulted negative. The results of the present study have demonstrated the efficiency of Forma™ IPL in terms of fungus deactivation and nail turbidity improvement, in chronic PSO and DLSO caused by *Trichphyton rubrum*. Different other factors might influence the efficiency of the treatment such as hygienic conditions, regularity in the application of topic antimycotic agents (prophylaxis), etc. Based on the encouraging results obtained in this research, it would be advisable to conduct further hospital study that can evaluate other aspects of clinical and statistical evidence, confirming the scientific validity to state this technological system as an elected therapeutic method in the treatment of Onychomycosis.

Bibliography

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