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Etiology and Management of Seborrheic Dermatitis

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Seborrheic dermatitis · *Malassezia* species · Antifungals

Abstract
Seborrheic dermatitis (SD) is a common dermatological disorder that varies greatly in severity between individuals and with time. The etiology of this disease is poorly understood. Early investigators focused on the role of *Malassezia* (previously *Pityrosporum*) yeasts in the development of SD. Some researchers have hypothesized that there is an immunological component to SD and that this disease is caused by an altered immune response to *Malassezia* yeasts. However, other researchers view this condition as the result of hyperproliferation. Both antifungal and anti-inflammatory preparations have been used to treat SD effectively and safely. The wide range of antifungal formulations available (creams, shampoos, oral drugs) provides safe, effective and flexible treatment options for SD.

Introduction

Seborrheic dermatitis (SD) is a common dermatosis, affecting between 1 and 3% of the immunocompetent adult population [1]. The incidence of this disease is much higher in immunocompromised patients, especially AIDS patients, ranging from 30 to 83% [2, 3].

SD is often seen in conjunction with other skin diseases, including rosacea, blepharitis and/or ocular irritation, acne vulgaris, pityriasis versicolor and *Malassezia* folliculitis [4–7]. The disease presents itself as red, flaking, greasy-looking patches of skin that are located most commonly on the scalp, nasolabial folds, eyebrows, ears and chest. The extent of flaking and erythema may vary in children and adults. It is somewhat more common in males than in females and tends to occur most frequently in adolescents and young adults, and again in adults over 50 years of age [8]. The disease appears to be influenced by seasons. The lesions worsen during winter, while sunlight seems to improve the clinical appearance of the disease.

Etiology

Correlation between SD and Malassezia *Yeasts*

In spite of the high global incidence of SD, few details are known about its etiology. A large majority of recent data supports a causal link between *Malassezia* and SD. This is because (i) antifungals have been found to be effective in treating SD and (ii) improvement in SD is accompanied by a reduction in *Malassezia* counts. Researchers have also tried to correlate the density of *Malassezia* with

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the clinical severity of SD and suggested that a reduction in *Malassezia* counts correlates with reduced SD flaking [9].

Malassezia *Species Associated with SD*

The species that have been shown to be most closely associated with SD to date are *M. globosa* and *M. restricta* [10, 11]. However, some authors have also reported *M. furfur, M. sympodialis*, *M. obtusa* and *M. slooffiae* [11]. Using a new technique, terminal fragment length polymorphism, Gemmer et al. [12] have shown that *M. restricta* and *M. globosa* are prevalent enough to be the cause of SD and/or dandruff. As for differences in species from lesional and nonlesional sites, while Nakabayashi et al. [11] found that *M. globosa* was isolated with the same frequency from both lesional and nonlesional skin, Gupta et al. [13] found that significantly more *Malassezia* yeasts could be cultured from nonlesional skin. Given that previous studies have failed to find this difference, the results of this study may represent an artifact of the sampling procedure. Gupta et al. [13] used contact plates filled with Leeming-Notman agar, while Nakabayashi et al. [11] utilized the swab and tape method. Further, Gupta et al. [13] have suggested that the use of synthetic detergents and shampoos by patients may represent factors that lead to reduced colony counts and hence differences in results in the various studies. There is also a possibility that SD of the scalp and the trunk may prove to be associated with different species, as there is evidence that different *Malassezia* species tend to be found on different body sites in both normal and diseased skin [13, 14].

Immune Response in SD

Because there are no clear differences in yeast carriage levels between SD patients and healthy controls, it has been suggested that a predisposition to this disease involves some sort of immune or inflammatory reaction. Even a normal number of *Malassezia* yeasts may trigger an inflammatory reaction [15]. A reaction between *M. furfur*, stratum corneum cells and the immune system in the follicles may be the primary trigger factor in SD [16]. Both cellular and humoral immunity have been investigated with regard to the pathogenesis of this disease. While Faergemann et al. [17] showed an increase in both lymphocyte transformation response and leukocyte migration inhibition in SD patients, Neuber et al. [18] found a reduced lymphocyte stimulation index when cells from SD patients were stimulated with *Pityrosporum ovale* extract. Faergemann et al. [17] detected increased numbers of NK1+ and CD16+ cells, in combination with complement activation, during their investigation of immune response of a sample of SD patients. In addition, elevated numbers of activated (HLA-DR4-positive) lymphocytes have been detected in the circulation of certain SD patients, prompting the hypothesis that intermittent activation of the immune system may have occurred [19].

In the inflammatory reaction of the skin, keratinocytes play an important role by secreting cytokines and adhesion molecules. Baroni et al. [20] determined the immunomodulatory and invasive capacity of *M. furfur* in a human keratinocyte cell culture. Their results support the hypothesis that *M. furfur* in vivo causes an initial break in the barrier function of the epidermis by inhibiting TGase I activity. They also demonstrated that actin fibers undergo evident changes during *M. furfur* penetration. Further, Watanabe et al. [21] have demonstrated that *Malassezia* yeast species can differentially induce human cytokine production by means of keratinocytes. The prevalence of SD has also been found to be greater in patients with AIDS. There is conflicting evidence regarding IgG antibodies in particular; some investigators have found an increase in IgG levels in patients [22] while others have shown that the elevated IgG antibody titers are not related to *Malassezia* [23]. Midgley [24] demonstrated that 72.5% of patients with SD had precipitating antibodies against *M. globosa*, in contrast to normal control subjects. Bergbrant et al. [25] studied the lymphocyte transformation response in SD patients to *M. furfur* antigens and found no difference when they compared it with controls. Differences in methods of antigen preparation may explain the variation in results of these studies. It has also been suggested that the lesions of SD are caused by toxin production or by the lipase activity of *Malassezia* [26]. The enzyme lipase splits triglycerides into fatty acids that may induce scaling [27] or releases arachidonic acid, which is involved in the inflammation of skin [28–30]. Taken as a whole, the above-cited studies strongly support the contention that *Malassezia* yeasts contribute to the pathogenesis of SD.

Several researchers have postulated that SD occurs as a result of hyperproliferation. This hypothesis is in part due to the effectiveness of keratolytic and anti-inflammatory agents (e.g. salicylic acid and corticosteroids) in the treatment of SD. Treatment with oral [31] and topical [32] ketoconazole improves the lesions of SD and reduces *Malassezia* counts on the skin. Further, it has been suggested that SD is not caused by an overgrowth of the *Malassezia* yeasts, but by an abnormal host response to the yeasts on the skin [23]. However, patients with SD do not appear to have higher total antibody levels than controls

[26]. Moreover, there is conflicting evidence regarding IgG antibodies in particular; some investigators have found an increase in IgG levels in patients [22], while others have shown that the elevated IgG antibody titers are not related to *Malassezia* [23]. Instead, it has been suggested that the lesions of SD are caused by toxin production or by the lipase activity of *Malassezia* [26]. The enzyme lipase splits triglycerides into irritant fatty acids that may induce scaling [27] or release arachidonic acid, which is involved in the inflammation of skin [28–30]. It has also been suggested that impaired cell-mediated immunity may facilitate fungal survival in the skin [33].

Therapy

Effective treatment of SD can occur with a wide range of material types, from selenium salts to highly specific azoles, and the functional link between these materials is antifungal activity [34]. *Malassezia* yeasts are susceptible to a wide range of nonspecific and antifungal topical treatments, and several effective oral agents are also available. Older treatments tended to lack antifungal activity and generally possess keratolytic properties. These agents include selenium sulfide [35], propylene glycol [36] and sulfur- and tar-containing compounds [37]. Presently, a wide variety of topical and systemic antifungal treatments are available for the therapeutic management and prophylaxis of SD. Specific antifungal agents used for the topical treatment of SD include zinc pyrithione [38], selenium sulfide [35], ciclopirox olamine [39], the azoles (ketoconazole [40, 41], bifonazole [42, 43], climbazole [44], metronidazole [45], miconazole [46], fluconazole [47], itraconazole [48]), terbinafine [49], butenafine [50], tacrolimus [51], pimecrolimus [52] and lithium gluconate [53, 54].

Mechanism of Action

Of the drugs cited above, the azoles represent the largest class of antifungals employed in the treatment of SD. Azoles inhibit the conversion of lanosterol to ergosterol, an essential component of the fungal cell membrane, by inhibiting the fungal cytochrome P450 (CYP450) enzyme lanosterol 14-α-demethylase [55, 56]. This is a fungistatic mechanism, resulting in the depletion of ergosterol and accumulation of sterol precursors, such as lanosterol. Itraconazole and fluconazole bind more weakly to human CYP450 than ketoconazole and thus cause fewer adverse events [57]. In addition to their antifungal properties, some azoles, including bifonazole, itraconazole and ketoconazole, have demonstrated anti-inflammatory activity [42, 48, 58].

Terbinafine is effective when applied topically and possibly when administered systemically [59, 60]. Terbinafine interferes with fungal sterol biosynthesis, specifically inhibiting squalene epoxidase leading to an intracellular accumulation of squalene [49]. This is a fungicidal mechanism. In contrast to the azoles, terbinafine does not involve CYP450 but inhibits ergosterol formation at an earlier stage [57]. Butenafine also has a similar mode of action.

Ciclopirox shows a good efficacy/tolerance ratio in mild to moderate SD [61]. Ciclopirox inhibits prostaglandin and leukotriene synthesis [62]. It may also exert anti-inflammatory effects by inhibition of 5-lipoxygenase and cyclo-oxygenase [63]. It acts through the inhibition of the uptake of essential compounds and at high concentrations also exerts an effect on the fungal cell membrane, altering cellular permeability [64].

It has been suggested that topical tacrolimus and pimecrolimus may be superior alternatives to corticosteroids as they both exhibit anti-inflammatory activity but do not have long-term side effects [51, 52]. Tacrolimus also exhibits antifungal properties as well as safety with respect to skin atrophy [51]. The mechanism of action of tacrolimus is fungicidal [65].

Nonspecific agents such as selenium sulfide, sulfur, coal tar and zinc pyrithione have a keratolytic mode of action. Zinc pyrithione has both nonspecific keratolytic and antifungal activity.

Prophylaxis

Since SD is a chronic, recurring anti-inflammatory skin disorder, attention must be given to a good efficacy/tolerance ratio, which reduces relapse and accommodates patient acceptance and compliance. Ketoconazole, miconazole and itraconazole are the preferred drugs in the prophylactic treatment of SD. The systemic antifungals that are used in therapy are ketoconazole, itraconazole and terbinafine. UVB (TL-01) phototherapy has also been shown to be effective in the treatment and prophylaxis of SD [66].

Conclusion

While SD has been a recognized clinical entity for decades, its etiology and relationship to other skin conditions are not very clear. The hypothesis that SD is primarily an inflammatory disorder, characterized by hyperproliferation of the stratum corneum, was increasingly popular in the past. This trend was also reflected in the common use of topical corticosteroids to treat SD. Since both antifungals and steroids result in clinical improvement of SD, we conclude that the original 'inflammatory or infectious' dichotomy was misguided and that the two alternatives are actually compatible. Antifungal agents are safe and effective in the treatment of SD; furthermore, they are widely available as creams, shampoos and oral formulations.

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