Is *Demodex folliculorum* an aetiological factor in seborrhoeic dermatitis?

Y. Karincaoglu, B. Tepe, B. Kalayci, M. Atambay* and M. Seyhan

*Departments of Dermatology and *Parasitology, Faculty of Medicine, Inonu University, Malatya, Turkey*

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Summary

Background. Seborrhoeic dermatitis (SD) is a common inflammatory skin disease for which no single cause has been found, although many factors have been implicated. The mite *Demodex folliculorum* (DF) is most commonly seen in the pilosebaceous unit in humans. SD is located in areas that are rich in sebaceous glands, which are also preferred by DF.

Aims. To compare the number of DF parasites in patients with clinical SD and in healthy controls, and to investigate any possible relationship between the number of DF mites and the presence of SD.

Methods. The study comprised 38 patients with SD and 38 healthy controls. Standard random and lesion-specific sampling was performed in the group of patients with SD, whereas standard random sampling only was performed for controls.

Results. *Demodex folliculorum* sampling was positive in 19 patients (50%) and 5 controls (13.1%). Mean DF density was $8.16 \pm 10.1/cm^2$ (range 0–40) and $1.03 \pm 2.17/cm^2$ (1–7) in patient and control groups, respectively. The differences between groups for DF positivity and mean DF density were significant ($P = 0.001$ for each). DF was found in 13 lesional areas in the patient group, but in only 5 areas in the control group ($P = 0.031$).

Conclusions. The number of DF mites was significantly higher in both lesional and nonlesional areas of patients with SD. This suggests that, when other aetiological causes are excluded, DF may have either direct or indirect role in the aetiology of SD.

Introduction

The *Demodex* mite is an asymptomatic, saprophytic ectoparasite that resides in hair follicles and sebaceous glands.[1,2] Only two types of *Demodex* have been identified in humans: *Demodex folliculorum* (DF) and *Demodex brevis* (DB).[1,3] Mites that spend their life cycles in pilosebaceous follicles use sebum and follicular cells as food.[1,4] DF, which is more common than DB, is generally localized to the infundibular area of the hair follicles, whereas DB is localized to sebaceous glands and ducts, which are deeper.[1,5] Both types of follicular mite are often seen on the face (the nasolabial fold, nose, cheeks, forehead, and eyelids) and rarely on the chest and scalp.[1,2,5] DF is the most common ectoparasite in humans.[6] The density of DF on healthy skin is normally $< 5/cm^2$.[7] DF is transmitted to newborns a few days after birth through breastfeeding or close physical contact;[1,8] however, DF density remains low through childhood, owing to low sebum production.[1] Its prevalence increases with age,[2,3] and may reach 100% in elderly adults.[3] It is believed that the increase in the number of DF or its penetration into the dermis causes infestation.[9] The classic clinical forms of DF infestation include pityriasis folliculorum, rosacea-like demodicidosis and demodicidosis gravis.[1,7] In addition, many other clinical forms of DF infestation have been reported in the

Correspondence: Dr Yelda Karincaoglu, Department of Dermatology, Faculty of Medicine, Inonu University, Malatya, Turkey.
E-mail: yeldakarincaoglu@hotmail.com

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literature, including pustular folliculitis, papulopustular scalp eruption, perioral granulomatous dermatitis, blepharitis, solitary granuloma, papular demodicidosis of the face, follicular spinulosus of the face, seborrhoeic dermatitis (SD)-like lesions, nonspecific facial pruritus with or without erythema, acneiform lesions, and *Demodex* granuloma.[1,5–8,10]

SD is a chronic and superficial inflammatory dermatosis of the skin. It is characterized by erythematous, thin, oily yellow squamae on the scalp, face, chest, back and flexural areas, which are rich in sebaceous glands.[11,12] It affects 1–3% of the population. Although many endogenous and exogenous factors including increased sebum activity, *Pityrosporum ovale* infection, drugs, immunological abnormalities, genetic predisposition, neurological disorders, emotional stress, diet, lifestyle and environmental factors have been implicated, the precise aetiology of SD is not known.[3–17]

SD is most commonly found on the scalp, nasolabial folds, ears, eyebrow and chest, where sebaceous glands abound. DF is also usually seen in follicles of the cheek, nose, forehead, chin, nasolabial fold and eyelid, where sebum is produced in great amounts. In our previous study,[7] we examined the clinical importance of DF in patients with nonspecific facial signs and symptoms, and found that, in addition to the well-known clinical conditions caused by this mite, DF could also cause SD-like erythematous, squamous pityriasiform lesions, suggesting that it may have a role in the aetiology of SD. Thus, this study examined the number and density of DF in lesional and nonlesional areas of patients who presented with SD and compared the results with healthy controls.

Methods

The ethics committee of Inonu University Faculty of Medicine approved the study, and written informed consent was obtained from all patients and controls.

The study comprised patients, either previously or newly diagnosed, presenting with SD to the Dermatology Clinic, İnönü University between February and June 2006. SD was diagnosed clinically. Patients who had pink, yellowish-brown, erythematous patch or plaque lesions covered with thin, oily and yellow squamae localized to the scalp, hairline, eyebrow, eyelashes, glabella, nasolabial fold, ears, external ear canal or breast cleavage were accepted as having classic SD. In total, there were 38 patients [8 women (21.1%), 30 men (78.9%); mean age 36.71 ± 13.20 years, range 16–73]. SD was localized to the scalp in 37 patients (97.3%), nasolabial fold in 34 (89.4%), eyebrow in 24 (63.1%), retroauricular area in 20 (52.6%), chest in 19 (50%) and eyelashes in 7 (18.4%). The number of SD lesional areas was 2 in 4 patients, 3 in 14 patients, 4 in 11 patients and 5 in 9 patients. The most common areas were the scalp and the nasolabial fold. The control group comprised 38 healthy people [11 (28.9%) women, 27 men (71.1%); mean age 55 ± 14.65 years, range 20–67], either medical students or hospital staff, who were matched for age and gender, did not have any disease, and were not receiving any systemic or topical treatment. Exclusion criteria were intertriginous involvement, age < 16 years, pregnancy or lactation, systemic corticosteroid or immunosuppressive treatment, radiotherapy or chemotherapy or topical acaricidal usage during the study period, and use of topical corticosteroids in the previous month.

Demodex folliculorum density was calculated as the number of mites per square centimetre of skin, with $\geq 5/cm^2$ area considered infestation. DF density was examined in both lesional areas (scalp, eyebrow, eyelash, retroauricular area, nasolabial folds and chest) and standard random areas (forehead, cheek, nose, chin and chest) in the patient group. Only standard random sampling was done in controls. DF was detected using a noninvasive method, standardized skin surface biopsy (SSSB). For SSSB, one side of a microscope slide is coated with a cyanoacrylate adhesive and the adhesive side pressed onto the lesion for 1 min, then peeled off. This procedure lifts off the top of pilosebaceous units, the surface keratin layer and their contents. In hairy areas such as the eyelashes, eyebrow and scalp, three hairs were removed, mounted on a slide and covered with glycerine, and examined for DF under light microscopy (× 40 and × 100 magnification), with a single mite being considered infestation.[9,18] Under microscopy, the mites, which were 0.3–0.4 mm long, had four pairs of short and long legs on the front part of the body.[3,5]

Statistical analysis

Results were compared with the control group. The independent samples *t*-test and Pearson's coefficient analysis were used.

Results

Demodex folliculorum was found in 19 patients (50%) and in 5 controls (13.1%). Mean DF density (evaluating lesional and standard random areas together) was $8.16 \pm 10.10/cm^2$ (range 0–40) in the patient group and $1.03 \pm 2.17/cm^2$ (1–7) in the control group.

Table 1 *Demodex follicurum* (DF) counts in patients with seborrhoeic dermatitis and controls.

	DF > 5/cm^2, *n* (%)	DF density per cm^2, mean ± SD (range)
Patients		
Both SD lesions and standard areas	19* (50)	8.16 ± 10.1/cm^2 (0–40)*
Only SD lesions	13† (34.2)	
Controls	5 (13.1)	1.03 ± 2.17/cm^2 (1–7)

*P = 0.001; †P = 0.031 (independent samples t-test).

Table 2 Frequency of *Demodex follicurum* (DF) (> 5/cm^2) in seborrhoeic dermatitis lesional areas.

Location	No. of DF-positive* lesional areas/total no. of lesional areas (%)
Scalp	5/37 (13.5)
Nasolabial fold	12/34 (35.2)
Eyebrow	2/24 (8.3)
Retroauricular	3/20 (15)
Chest	0/19 (0)
Eyelash	2/7 (28.5)

*> 5/cm^2.

Table 3 Frequency of *Demodex follicurum* (> 5/cm^2) in standard random areas of the face and chest in patients with seborrhoeic dermatitis.

Location	No. of patients (%)
Cheek	17 (44.7)
Forehead	15 (39.5)
Nose	9 (23.7)
Chin	7 (18.4)
Chest	0 (0)

The number of DF-positive patients and the mean DF density were significantly higher in the patient group than in the controls in both lesional and nonlesional areas (P = 0.001 for both). When only lesional areas were evaluated in the patient group, DF was positive in 13 (34.2%) patients, and the difference between the patient and control group was again significant (P = 0.031). The number and density of DF in the patient and control groups are presented in Table 1. The number of lesions positive for DF was 5 (13.5%) on the scalp, 12 (31.6%) on the nasolabial folds, 2 (5.3%) on the eyebrow, 2 (5.3%) on the eyelashes, 3 (7.9%) on the retroauricular area and 0 on the chest (Table 2). Using standard random sampling of patients, DF was positive in 17 (44.7%) areas on the cheek, 15 (39.5%) on the forehead, 8 (23.7) on the nose and 7 (18.4) on the chin; no area on the chest was positive (Table 3).

Discussion

SD is a well-known condition with variable severity and unclear aetiology. The variety of proposed causes support the notion that the condition is more complex than an 'oily inflammation of the skin'.[14] SD seen in sebaceous gland-rich areas has been attributed to the increased activity of these glands. Activation of sebaceous glands in puberty explains why SD is common in adolescents and young adults. In addition, the androgen-associated hormonal factors affecting pilosebaceous units explains why the disease is more common in male patients.[14,15] However, SD does not develop in all young adults who have a greasy skin, and the sebum secretion rate of patients with SD can be within the normal range. Therefore, it is believed that rather than being a primary aetiological factor, seborrhoea is a predisposing factor for SD and that SD is not a disease of the sebaceous glands.[15]

The proposal that SD is a superficial fungal disease of the skin developing in sebaceous gland-rich areas has risen from the relationship between Malassezia yeasts and SD.[16,19] *Pityrosporum ovale* is a lipophilic yeast of the Malassezia genus. These yeasts, which are members of the natural flora of the skin, are found in seborrhoeic areas of the body.[13] Owing to their lipase activity, they break down triglycerides into irritant fatty acids that can form desquamation and bring about SD lesions.[20] The number of these yeasts is raised in SD and can be cultured from the lesions.[15] Mirza *et al.*[21] showed that *Pityrosporum* yeasts were higher both in native preparations and in the culture of patients with SD relative to normal individuals and thus, colonization rate increased in SD. Antifungals are effective in the treatment of SD by reducing the number of yeasts, further supporting the involvement of *Pityrosporum ovale* in the aetiology.[13,14,17] Although a correlation between SD severity and yeast density was reported, it was also reported that the number of Malassezia yeasts in patients with SD was not higher than that in controls and that the response to antifungals resulted from the anti-inflammatory effects of the drugs.[15] Furthermore, it was suggested that SD is associated with an abnormal response of the host to the yeasts, but the antibody level was not found to be higher than controls.[14–16] However, it was also suggested that the inflammation was started by reactivation of an immune reaction to antigens produced by *Pityrosporum ovale* or their toxic products and the secretion of some cytokines from the keratinocytes.[14,15]

DF, which is a saprophytic mite of human pilosebaceous units, can be found anywhere on the skin, but primarily on the forehead, cheek, nose, nasolabial fold and eyelid, where sebum production is profuse.[22] It has also been found on the scalp, neck, chest, nipple, penis, mons veneris, hip and buccal mucosa, where ectopic sebaceous glands abound.[3,23] Its presence in healthy individuals suggests the possibility of transmission through contact. Examination of skin biopsies can reveal DF at rates as high as 20–30%. It was established in one study that 10% of 1124 skin biopsies and 12% of 1692 follicles contained follicular mites.[6,22]

The cause of the clinical features in DF infestation is still not known. The hypotheses include immunological deficiency or abnormal immunological reaction of the skin to the parasite.[22] Various explanations have also been put forward for the pathogenic mechanisms: (i) the obstruction of sebaceous canals and follicles by the mite can lead to epithelial hyperplasia, reactive hyperkeratinization and blockage of secretion in addition to increase in bacteria colonization; (ii) there may be a foreign-body reaction to the chitinous skeletons of the mites; or (iii) mites and their discharge products can stimulate humoral and cellular immune reactions and set off inflammation.[1] Georgala *et al.*[24] support the hypothesis that *Demodex* infestation is a type 4 delayed hypersensitivity reaction to an unknown antigen of mite or follicular origin. According to Akilov and Mumcuoglu,[4] as mites cannot penetrate into the basal membrane, they do not encounter the immune system of the skin and therefore the disease develops only in genetically predisposed individuals, hence the reason that the incidence of the disease is higher in patients who have human leucocyte antigen (HLA)-Cw2 and HLA-Cw4 alleles. When planning this study, we did not believe that HLA testing would be feasible without proving the relationship between SD and DF, but our results now suggest that HLA testing may be a useful technique for further study.

Two clinical forms of *Demodex* infestation in humans were first defined in 1930 by Ayres. Pityriasis folliculorum particularly affects women of middle age or older. It is characterized by diffuse, but dull facial erythema, itching and a burning sensation, thin follicular plugs, and squamae that look like sandpaper.[10] Rosacea-like demodicidosis (RLD) clinically resembles rosacea. It is characterized by erythematous and squamous papulopustules on the cheek, perioral area and back of the nose.[22] Lesions are superficial and there is a tendency toward minor papulovesicular and vesiculopustular formation. Additionally, RLD starts abruptly and progresses rapidly. There is no previous flushing, persistent erythema, photosensitivity, sebostatic skin type, tingling or burning sensation, or telangiectasia.[7,10] Demodicidosis gravis, on the other hand, resembles severe granulomatous rosacea. It involves dermal granulomata, central caseation necrosis and mite discharges phagocyosed by foreign body giant cells.[1] A multitude of clinical variants of DF, such as papulopustular scalp eruption, perioral granulomatous dermatitis, blepharitis, solitary granuloma, papular demodicidosis of the face, follicular spinulosus of the face, SD-like lesions, nonspecific facial pruritus with or without erythema, acneiform lesions, *Demodex* granuloma and dermatitis rosaceiformis steroidica have been reported.[1,5–8,10]

In our study, the lesional and nonlesional areas in patients had DF counts and density that were significantly higher than controls. When only lesional areas were evaluated in patients with SD, the number of DF-positive areas was still significantly higher. Thus, it is likely that the explanations for how DF causes SD are similar to those put forward for Malassezia.[9] Reactivation of the immune system by antigens derived from DF or its toxic products can stimulate inflammation, and secretion of cytokines from keratinocytes may induce or aggravate SD. It is possible, however, that SD may be the predisposing factor to DF infestation, instead of the result of such infestation, although there is no support for this possibility in the literature. A possible explanation for the high DF numbers in non-SD areas in patients may be local parasite migration or contact transmission (i.e., by itching).

In conclusion, detection of pathogenic numbers of DF in SD-like pityriasiform lesions of patients presenting with atypical facial signs and symptoms, as described in our previous study, may indicate that DF can have many clinical presentations. The significantly higher numbers of DF in lesional and nonlesional areas of patients with SD compared with controls in the current study supports this idea. Although various theories exist as to the aetiology of SD, its precise aetiology and its relationship with other skin diseases is not yet clear. However, given the results of our study, we believe that DF can play a direct or indirect role in the aetiology of SD in patients in whom other causes cannot be identified. Further studies into the possible role of DF in SD and into the positive results obtained in response to acaricidal treatments in DF-positive patients with SD are needed.

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