

Blepharitis and *Demodex* spp. infection

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ABSTRACT

According to the latest reports *Demodex* mites appear to play an important role in the pathogenesis of chronic blepharitis. *Demodex* mites are cosmopolitan and are present in many species of mammals. In this paper we describe two species that are found in humans: *Demodex folliculorum* and *D. brevis*. Infection occurs during direct contact with an affected person and also through contact with dust containing eggs of the parasite, through contact with bed linen, as well as cosmetics used together with an affected person. Treatment of chronic blepharitis caused by *D. folliculorum* and *D. brevis* is difficult and time consuming. Some improvement can be achieved after topical application of yellow mercury ointment, sulphuric ointment, camphor oil, crotamiton, cholinesterase inhibitors, sulfacetamide, steroids, antibiotics and antifungal drugs. Good results have been achieved with oral ivermectin and permethrin cream. However, the best results were observed after treatment with metronidazole.

KEY WORDS: pathogenesis, infection, ocular demodicosis, treatment

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INTRODUCTION

Blepharitis can be caused by bacterial or fungal infection, allergic reaction, metabolic disease, uncorrected refractive errors, and *Demodex* spp. Anterior blepharitis is usually caused by staphylococcal infection, while posterior blepharitis is usually related to meibomian gland dysfunction or seborrheic blepharoconjunctivitis. Recent reports have highlighted the importance of *Demodex* mites in the pathogenesis of chronic blepharitis, especially in cases with weak reaction to treatment. Recurrent hordeola and chalazia can be a result of *Demodex* spp. infection [1].

Demodex mites are cosmopolitan and are therefore found in different species of mammals. At the time of writing, two species have been found in humans: *Demodex brevis* (Akbulatova, 1963) and *D. folliculorum* (Simon, 1842). Recently these two species have been classified as parasites after previously being described as commensals [2]. However, the pathogenicity of these two species of mites is con-

troversial because they can also be found in healthy individuals [3]. Based on the results of current studies, it is estimated that *Demodex* mites are present in 10% of healthy people and can be found in 12% of their hair follicles [4]. It is postulated that *D. folliculorum* becomes pathogenic when it reproduces intensively, causing increasing ocular symptoms [5].

BIOLOGICAL PROPERTIES

Demodex mites have a vermiform shape and are covered by a thin cuticle (Fig. 1). *Demodex folliculorum* are larger (0.3–0.4 mm) and are more elongated. They live in larger groups in the orifices of hair follicles. *Demodex brevis* is smaller (0.2–0.3 mm) and has a fusiform shape and short legs. It can be found in single sebaceous glands throughout the facial skin and also in the meibomian glands of the eyelids [6]. The body of *Demodex* mites can be divided into the gnathosoma with the mouthpart, the podosome, and the opisthosoma. In both

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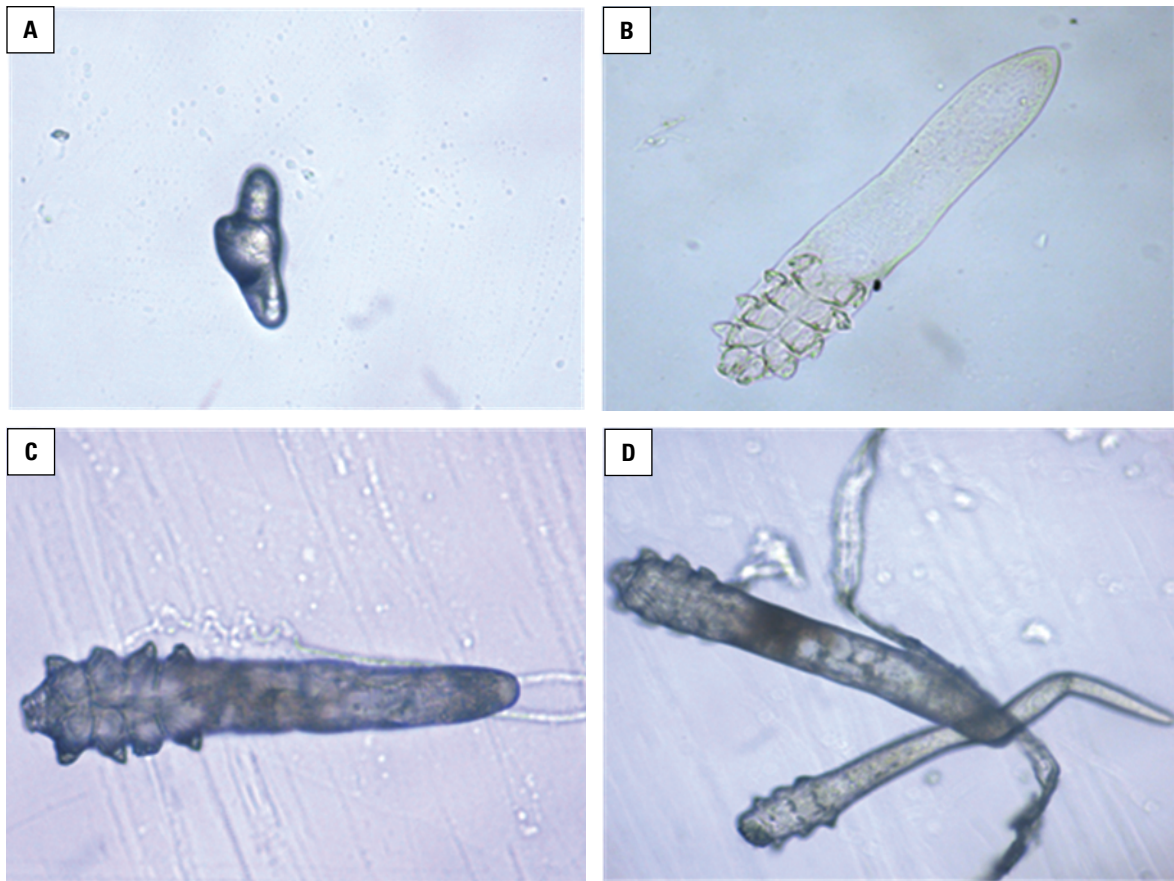


FIGURE 1. Developmental stages of *Demodex folliculorum*: **A** — egg; **B–D** — adults (magnification 100×)

species the podosome has four pairs of legs and three pairs in larvae. The gnathosoma of *D. folliculorum* contains sharp and more dagger-like mandibles than in *D. brevis*, which serve to take up food, and palps that are necessary to hold food. The mandibles serve to cut the epithelium of the hosts skin. The parasites excrete enzymes that can initially digest food, after which the mites suck it in. This form of feeding causes the destruction of the epithelium and the penetration of the parasite into the deeper layers of the skin. The main food source in all stages of development are the components of serum. As a result, the parasites thrive in areas that are especially rich in sebaceous glands [7–8]. The life cycle of *D. folliculorum* lasts between 14 and 18 days. The development is simple and it occurs in only one host. The female lays eggs, from which larvae initially without legs hatch. The larvae then develop three pairs of unsegmented legs. After the first moulting, the larvae transform into an eight-legged nymph, and after another two moultings into an adult form, either female or male [9].

Demodex spp. is sensitive to changes in temperature and pH. The optimal temperature for the de-

velopment of *Demodex* spp. ranges from 16 to 20°C. The parasites stop feeding at temperatures below 0°C or above 37°C. At temperatures above 54–58°C they die. *Demodex* mites prefer an acidic environment and are sensitive to UV radiation [10–11].

EPIDEMIOLOGY

Demodex folliculorum and *D. brevis* most often occur in elderly patients. Cheng et al. [12] found a prevalence rate of 84% in a population aged 60 years and almost 100% in a population over 70 years old. Garbacewicz et al. [13] noted a low prevalence in young people (5%), which can probably be attributed to excretion of smaller amounts of sebum by the sebaceous glands of Zeiss and the Meibomian tarsal glands in children and teenagers [11].

Infection occurs through direct contact with an affected person and most likely through contact with dust containing eggs of the parasite, through contact with bed linen, or by sharing the same cosmetics with an affected person [14–15]. Moreover,

it has been discovered that eggs of *Demodex* spp. can be found in microscope eyepieces. The results of studies carried out by Garbacewicz et al. [13] showed that 30% of people using a microscope were infected with *Demodex* spp.

The factors having an influence on *Demodex* spp. infection are profession, type of skin, dermatological illnesses, living standards, housing and work place standards, as well as personal hygiene habits [8]. Wesołowska et al. [16] found that *Demodex* spp. occurs in 40% of people of a medical profession such as doctors, nurses, and physiotherapists, and in 33.7% of medical students and 23.5% of drug abusers. Ocular demodicosis can be a result of the presence of mites on the facial skin [17–18]. *Demodex* spp. infection has been observed in 47% of people with oily skin, in 26.6% of people with dry skin, and in 33.9% of people with a mixed complexion. People with dermatological illnesses such as rosacea and skin acne are more susceptible to *Demodex* spp. infection (62%) than healthy people (27.6%). A higher infection rate has been also observed in patients living in areas of humid climate (67.9%) than in people living in areas of dry climate (24.5%) [19]. Wesołowska et al. [16] described a higher prevalence of *Demodex* spp. infection among people living in older housing (43.5%) than among people living in newer housing (39.4%). However, the difference was not statistically significant.

Some researchers have described the prevalence of *Demodex* spp. infection to be related to the sex of the examined patients. Raszeja-Kotelba et al. [20] and Forton et al. [21] have given a higher intensity of infection in women than in men, which was attributed to the use of creams and powders as well as being influenced by sex hormones. However, Horváth et al. [22] observed that the infection rate was higher in men than in women. Yamashita et al. [23] and Kuźna-Grygiel et al. [14] as well as Wesołowska et al. [16] did not find a relationship between sex and the prevalence of *Demodex* spp. infection. Dokuyucu et al. [24] examined the correlation of *D. folliculorum* infection and the body mass index (BMI). The results indicated that increased BMI influenced the prevalence of *Demodex* spp. infection. 26.3% of overweight or obese patients (BMI > 35) had *D. folliculorum*. A higher prevalence was also found in underweight patients (13.3%). However, Gökçe et al. [25] did not find any relationship between the prevalence of *D. folliculorum* and BMI.

It has also been observed that *Demodex* spp. occurs more often in patients with lower immunity [26, 27].

Demodex spp. infection has been noted in patients with HIV, leukaemia, or cancer [28, 29]. *Demodex* spp. has been diagnosed in patients with diabetes, renal failure, and in patients undergoing haemodialysis [3, 25, 28, 30].

There are publications proving a relationship between *Demodex* spp. infection and blepharitis. Tian and Chao-Pin [31] examined 507 patients with blepharitis and noted that 50.7% of patients have *Demodex* spp. The authors also observed *Demodex* spp. in 58 patients (11.7%) with other eye diseases. Türk et al. [32] observed *D. folliculorum* in 29.7% of patients with blepharitis, in 9.1% of patients with blepharoconjunctivitis, and in 4.2% of patients in a control group. Bhandari and Reddy [5] discovered the mites in 78.7% of people with chronic blepharitis. However, Kemal et al. [33] did not observe any statistically significant difference of the prevalence of *Demodex* spp. in patients with and without blepharitis. Wesołowska et al. [16] similarly did not observe any higher prevalence of demodicosis in people wearing eyeglasses or contact lenses.

PATHOGENESIS

Demodex mites feed on the cells lining hair follicles. Metabolites and undigested leftovers can accumulate at the base of eyelashes and create cylindrical dandruff, which is pathognomonic for ocular demodicosis [12]. *Demodex* spp. mechanically block sebaceous glands, irritate the eyelids, and induce hypertrophy of the epithelium and hyperkeratinisation. *Demodex* spp. may induce in the host a granulomatous inflammation and immunologic response [34–35]. Köksal et al. [36] have observed a granuloma within a Meibomian gland harbouring *Demodex* spp. and surrounded by epithelial cells, stromal cells, fibroblasts, lymphocytes, and plasmatoc cells. In studies carried out by Liang et al. [37] demodicosis was found along with chalazia 69.2% more often than in the control group (20.3%). Additionally, patients with demodicosis had a tendency to relapse (33.3%), especially those infected with *D. brevis*, which is more often found than *D. folliculorum* in patients with chalazia.

Yam et al. [38] discovered *Demodex* mites in 72.9% of patients with recurrent chalazia. They concluded that recurrent chalazia is associated with ocular demodicosis.

Past studies have shown that in the aqueous humour of patients infected with *Demodex* spp. there is more interleukin 17 (IL-17), which causes

inflammation and blockage of the glands. In addition, it can cause damage to the eye surface [39–40]. Akilov and Mumcuoglu [41] have shown that in people with demodicosis, the level of CD95+ is elevated, while CD3+, CD4+, CD8+, CD16+, and the CD3+/CD20+ ratio is lower. No difference in the concentrations of IgA, IgM, and IgG has been found. Kim et al. [39] examined the clinical and immunological response to *Demodex* spp. infection. A significant decrease in IL-1 β and IL-17 was observed in patients receiving treatment. The level of IL-5, IL-7, IL-12, IL-13, G-CSF, and MIP-1 β also decreased; however, the difference was not statistically significant. *Demodex* mites can avoid or suppress the immunological response of the host by inhibiting all three pathways of the complement system (classical, lectin and alternative) through scabies mite-inactivated serine protease paralogues and serine protease inhibitors [29].

SYMPTOMS

The clinical symptoms of ocular demodicosis are uncharacteristic and patients are frequently asymptomatic. Gao et al. [42] noted a correlation between the number of *Demodex* mites and the intensity of symptoms. Patients with blepharitis and diagnosed presence of *Demodex* mites have complained of symptoms such as: itchiness, a burning sensation, a feeling of heavy eyelids, excessive lacrimation, and the presence of mucous discharge [5]. Other symptoms of ocular demodicosis may include eyelid and conjunctival hyperaemia, madarosis, loss of eyebrows, photophobia, and excessive sensitivity to smoke and dust [11]. Gao et al. [42] noted Meibomian gland dysfunction in 63.6% and loss of eyelashes in 45.5% of people with diagnosed eyelid demodicosis. Kheirkhah et al. [43] observed meibomian gland dysfunction in 83.3%, rosacea in 66.7%, and decreased vision in 50% of patients with blepharitis caused by *Demodex* mites. Inceboz et al. [44] observed itchiness (61.7%) and hyperaemia (59.1%) in patients with *D. folliculorum*.

Untreated ocular demodicosis may lead to serious complications. Inflammation caused by a large number of parasites and serious symptoms of blepharitis may affect the cornea, conjunctiva, and cause neovascularisation, conjunctival hyperaemia, and conjunctiva of nipple follicles [8]. Patients treated using antibiotics or antiviral drugs may note a short improvement and decrease in symptoms. However, a delay in providing appropriate treatment may ulti-

mately lead to corneal ulceration, corneal clouding, or the formation of white spots, which have a significant influence on visual acuity [8].

DEMODEX SPP. AS A VECTOR

It has been established that *Demodex* mites take part in the transmission of pathogens, which may play a prominent role in the pathogenesis of demodicosis [45]. Symptomatic demodicosis often coexists with bacterial infections, which can be confirmed by the decreasing number of *Demodex* mites after the treatment of patients with acne using tetracyclines [46]. Spickett [47] noted that *D. folliculorum* may be a vector organism for *Mycobacterium leprae* bacilli. Lacey et al. [48] isolated *Bacillus oleronius* from within the *D. folliculorum* of a patient of acne rosacea and specific antigens from the serum of examined patients. Similar results were reported by Szkaradkiewicz et al. [49]. They described both *Demodex* spp. and *B. oleronius* in patients with acute blepharitis. Clifford et al. [50] noted the coexistence of *Staphylococcus aureus* and *D. folliculorum* in patients with diabetes; however, such a situation was not described by Lee et al. [51]. *Demodex* spp. can take part in the transmission of fungi [52]. Hallur et al. [53] described a coinfection of *D. folliculorum* and *Apophysomyces elegant* in patients with decreased resistance.

DIAGNOSIS

In the diagnosis of ocular demodicosis, eyelashes are examined — a few are taken aseptically from both eyelids of both eyes. The material is examined under a light microscope at 100 \times magnification. It can be also examined in saline at 25 \times magnification. If cylindrical dandruff is present, 20 μ L of 100% alcohol or a 0.25% solution of fluorescein drops should be pipetted into the edge of the coverslip to enable the migration of the parasite. The time of examination extends to 20 minutes [17]. In the case of recurrent chalazia, the lesions can be taken for histopathological examination to determine the presence of *Demodex* mites [8].

TREATMENT

Treatment of chronic blepharitis caused by *D. folliculorum* and *D. brevis* is difficult and time consuming. Some improvement can be achieved after topical application of yellow mercury ointment, sulphuric ointment, camphor oil, crotamiton, cho-

linesterase inhibitors, sulfacetamide, steroids, antibiotics, and antifungal drugs. Good results have been achieved with simultaneous oral ivermectin and permethrin cream [54–55]. Filho et al. [56] examined the effectiveness of oral ivermectin in patients with blepharitis with proven *Demodex* spp. infestation. Complete resolution was achieved 90 days after initiation of treatment independently of the intensity of the infection. Brown et al. [57] noted the case of a 12-year-old girl with serious ocular demodicosis and rosacea, who improved a month after receiving single-dose 12-mg therapy with ivermectin.

However, we obtained the best results after treatment with metronidazole. Therefore, we encourage the use of the following ointments:

- Metronidazoli — 0.5;
- Glycerini — 2.0;
- Vaseline albi ad — 20.0;
- M. f. unq. ophthalmicum;
- S — twice daily on eyelid margins;

and:

- Metronidazoli — 3.0;
- Hascobaza — 100.0;
- M. f. unq.;
- S — twice daily on face.

The treatment of ocular demodicosis takes between two and three months. Subsequently we check whether the parasite is still present. If *Demodex* spp. can still be found, then the treatment is continued for another 2–3 months [58].

A prepared formula of Spanish sage oil and lyophilised aloe is available on the market. Special handkerchiefs and solutions can be used in maintaining eyelid hygiene. The symptoms of ocular demodicosis can be alleviated by sunbathing, washing the skin of the face with a mixture of warm water and hexachlorobenzene.

The prophylaxis of *Demodex* spp. infection consists of rigorous eyelid care, improvement of personal hygiene, and not sharing towels and cosmetics with people infected with *Demodex* spp.

However, the role of *Demodex* spp. as a commensal should not be overlooked. Treatment should not be aimed at total eradication of the mite but rather restoration of the ocular ecology to a balanced state [59].

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