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Ocular Demodicosis as a Potential Cause of Ocular Surface Inflammation

Xiaohui Luo, MD*, Jing Li, MD*, Chuan Chen, MD*, Scheffer Tseng, MD, PhD^{†,‡}, and Lingyi Liang, MD, PhD*

*State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Ocular Surface Center, Sun Yat-sen University, Guangzhou, China

[†]Ocular Surface Center, Miami, FL, USA

[‡]Tissue Tech Inc., Miami, FL, USA

Abstract

Among different species of mites, *Demodex folliculorum* and *Demodex brevis* are the only two that affect the human eye. Because demodicosis is highly age-dependent and can be found in asymptomatic adults, the pathogenicity of these mites has long been debated. Herein, we summarize our research experience including our most recent study regarding *Demodex* infestation as a potential cause of ocular inflammatory diseases. Specifically, we describe the pathogenesis of demodicosis and then discuss the results of work investigating the associations and relationships between ocular demodicosis and blepharitis, meibomian gland diseases, and keratitis, in turn. This is followed by some discussion of the diagnosis of demodicosis, and concludes with a brief discussion of the evidence for different treatments for ocular demodicosis. Collectively, our studies suggest a strong correlation between ocular demodicosis and ocular surface inflammatory conditions, such as blepharitis, chalazia, MGD, and keratitis. Further investigation of the underlying pathogenic mechanism is warranted.

Keywords

Demodex mite; ocular surface; inflammation

INTRODUCTION

Demodex, a genus of small parasitic mites affecting mammals, was first identified in 1841, but has only recently attracted attention from clinicians including ophthalmologists, dermatologists, and other specialists. Among different species of mites, *Demodex folliculorum* and *Demodex brevis* are the only two that affect human skin (Figure 1). As the eye is surrounded by protruding body parts, such as the nose, brow, and cheek, it is not as

Corresponding Author: Lingyi Liang MD, PhD, State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Ocular Surface Center, Sun Yat-sen University, 54S Xianlie Road, Guangzhou 510060, China. Tel: +8613829738319, lingyiliang@qq.com.

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accessible as the rest of the body to daily hygiene. Therefore, after *Demodex* infestation occurs in the facial skin, it is likely to spread and flourish in the eye, resulting in ocular demodicosis.¹ The morphologies and habitats of the two *Demodex* mites are different. The larger one, *D. folliculorum* (Figure 1A) at about 0.3–0.4 mm long, congregates as a group in the hair follicle, while the smaller one, *D. brevis* (Figure 1B) at about 0.2–0.3 mm long, resides solitarily in the sebaceous gland.^{1–3} Hence, when eyelashes are sampled, the chance of detecting *D. folliculorum* is much greater than the chance of detecting *D. brevis* in the general population and in patients with blepharitis.⁴ The lifespan of *Demodex* mites is about 3–4 weeks from the egg stage to the adult stage.⁵ Females may live an additional 5 days after oviposition.⁵

The rate of *Demodex* infestation increases with age, being observed in 84% of the general population aged 60 years and 100% of the general population aged above 70 years.⁶ There are some risk factors that may predispose patients to the development of ocular demodicosis such as rosacea, skin phototype, sunlight exposure, alcohol intake, smoking, stress, hot beverages, spicy food, abrupt changes in temperature,^{7,8} and systemic immunocompromised status.⁹

In the dermatology literature, *Demodex* mites have been suggested as causes of certain skin diseases, such as pityriasis folliculorum, perioral dermatitis, scabies-like eruptions, facial pigmentation, eruptions of the bald scalp, demodicosis gravis, and even basal cell carcinoma.^{10,11} Besides skin disorders, ocular demodicosis has been implicated in a number of external eye diseases, such as eyelash loss, abnormal eyelash alignment, blepharitis, conjunctivitis and blepharoconjunctivitis.^{1,12–15} Interestingly, demodicosis has also been associated with pterygium, meibomian gland dysfunction (MGD), sight-threatening keratitis, and eyelid basal cell carcinoma.^{16,17}

PATHOGENESIS

The pathogenesis of *Demodex* mites has been debated for a long time.^{18–20} This is partly because demodicosis has a high age-dependent prevalence and is frequently found in the skin of asymptomatic individuals.^{21,22} In the eye, a similar debate has been raised for blepharitis.¹ It is postulated that *Demodex* mites become pathogenic when they multiply and cause or exacerbate ocular symptoms and eyelid margin changes. However, no previous research has convincingly demonstrated whether a minimal number of mites must be present to produce symptoms. As humans are the only host of *Demodex* mites, no animal models of ocular demodicosis have been successfully established. A prospective cohort or controlled study focusing on young patients, in which *Demodex* infestation is believed to be rare, would support their pathogenic role in demodicosis. The possible causative relationship between *Demodex* infestation and ocular inflammation could be further supported if the inflammation resolves after mite-killing therapy.

A plausible action mechanism for *Demodex* infestation involves causing direct damage, acting as a vector for bacteria, and inducing hypersensitivity. First, *Demodex* mites, especially *D. folliculorum*, consume epithelial cells at the hair follicle, resulting in follicular distention. Microabrasions caused by the mite claws further induce epithelial hyperplasia

and reactive hyperkeratinization.^{23,24} Meanwhile, *D. brevis* usually burrows deep into the meibomian glands. Besides mechanically blocking the orifices of the meibomian glands, its chitinous exoskeleton may act as a foreign body and cause granulomatous reactions.^{25,26} Thus, *Demodex* mites may be a potential cause of chalazia and MGD.¹² Second, *Demodex* mites carry concomitant bacteria such as *Streptococci* and *Staphylococci* on their surface, as well as *Bacillus oleronius* inside their abdomen.^{14,24,27} Third, the proteins inside the mites and their debris or waste may trigger host inflammatory responses through delayed hypersensitivity or innate immune responses.^{24,28}

OCULAR DEMODICOSIS AND BLEPHARITIS

The first documented disorder associated with demodicosis was blepharitis, which can be dated as early as 1899. The most common clinical manifestations of blepharitis associated with demodicosis include chronic and recurrent inflammation of the eyelid margin with a variety of eyelash malalignments, such as trichiasis, distichiasis, madarosis, and typical cylindrical dandruff (CD) around the eyelash root. Successful diagnosis and subsequent treatment of ocular demodicosis lead to quick resolution of blepharitis in adult patients when traditional therapies fail (Figure 2).^{12,16}

As mentioned above, it is generally believed that *Demodex* infestation is common in adults, but no mites are found in individuals aged under 16 years.^{21,29,30} Although *Demodex* has been implicated as a potential cause of blepharitis in adults,^{12,16,29,31–33} no studies have demonstrated whether the mites also infest eyelashes in children with blepharitis. Furthermore, all pediatric cases of dermatological demodicosis develop in patients with compromised local or systemic immune status by topical or systemic administration of steroids or other immunosuppressive agents^{10,34,35} or by leukemia or HIV.^{36–39} Therefore, unsurprisingly, most physicians do not consider ocular demodicosis as a cause of blepharitis in healthy pediatric patients.

However, we detected ocular *Demodex* infestation in 12 systemically healthy pediatric patients.¹³ The patients comprised 7 females and 5 males, with a mean age of 7.5 ± 2.5 years (range, 2.5–11 years). All 12 patients experienced acute episodes of severe ocular surface inflammation previously diagnosed as blepharitis or blepharoconjunctivitis. None of the patients had responded to prolonged broad-spectrum antibiotic regimens. However, an eyelid scrub with 50% tea tree oil (TTO) or eyelid massage with 5% TTO ointment resulted in dramatic alleviation of symptoms and marked resolution of inflammatory signs. These beneficial effects were associated with disappearance of CD in eyelashes and decreased *Demodex* counts. Collectively, the findings suggest that ocular *Demodex* infestation can be detected in children presenting with blepharitis during their first decade of life. Furthermore, for the first time, the findings demonstrate that demodicosis leads to ocular surface diseases even in pediatric patients who are not immunocompromised.

OCULAR DEMODICOSIS AND MEIBOMIAN GLAND DISEASES

The key pathologic finding for chalazion is chronic inflammatory granuloma in the meibomian gland, a specialized sebaceous gland in the eyelid.⁴⁰ Based on the presence of

giant cell infiltration in the chronic inflammatory granuloma, many suspect that chalazion is caused by host response to a foreign body derived from several pathogens. Intriguingly, in our pediatric demodicosis study described above, one-third (4/12) of the patients presented with recurrent chalazia, in addition to blepharitis.¹³ It is known that *D. brevis* resides deep in sebaceous glands, including the meibomian gland. Thus, we wondered whether ocular demodicosis could play a role in chalazia. To address this issue, we conducted a prospective and comparative study on the possible correlation between ocular demodicosis and chalazia.⁴

The study group comprised 91 consecutive patients with chalazia. As demodicosis is common in adults,⁶ the study group was further divided into a subgroup of 47 pediatric patients aged under 14 years and a subgroup of 44 adult patients aged above 15 years, to minimize the bias. The age- and sex-matched control groups comprised 30 pediatric patients and 43 adult patients with no past history or present illness of chalazia. Demodicosis was detected in 63 of 91 patients (69.2%) in the study group, being significantly more prevalent than the 13 of 64 patients (20.3%) in the control group ($P<0.001$). When the patients were subdivided into the pediatric and adult subgroups, demodicosis was still significantly more prevalent in patients with chalazia (70.2% and 68.2%, respectively) than in control patients (13.3% and 26.5%, both $P<0.001$). The same results were obtained when demodicosis was measured by *Demodex* counts (2.8 ± 3.2 in study group vs. 0.5 ± 1.4 in control group, $P<0.001$). The differences from the control group was remained significant for both the pediatric subgroup (2.6 ± 3.2 , $n=47$ vs. 0.1 ± 0.4 , $n=30$, $P<0.001$) and the adult subgroup (3 ± 3.2 , $n=44$ vs. 0.9 ± 1.8 , $n=43$, $P<0.001$).

We further examined the relative importance of *D. folliculorum* and *D. brevis*. Our results showed that *D. brevis* had a higher odds ratio than *D. folliculorum* (18.2 vs. 2.8), suggesting that *D. brevis* may play a more important role than *D. folliculorum* in chalazia. Interestingly, among 74 patients who underwent surgery with a follow-up period of 14 ± 5.3 months, recurrences were noted in 15 of 45 patients (33.3%) with demodicosis, being significantly higher than the 3 of 29 patients (10.3%) without demodicosis ($P=0.02$). The above data indicated that ocular demodicosis, especially with *D. brevis*, was significantly more prevalent in patients with chalazia, and that patients with ocular demodicosis, especially with *D. brevis*, tended to experience recurrence after surgical treatment.

MGD is another very common meibomian gland disease. Therefore, we speculated that ocular demodicosis may also be found more often in patients with MGD. To test this hypothesis, we recently conducted a prospective controlled study (unpublished findings) focusing on 60 patients with demodicosis, who were all aged under 35 years to mitigate any concern over the high prevalence of demodicosis in older populations also showing prevalence of MGD. The control group comprised 45 sex- and age-matched dry eye patients without demodicosis. The diagnosis of MGD was first made clinically by the presence of ocular symptoms as well as by external and slit-lamp examinations to detect one or more eyelid margin abnormalities (irregular eyelid margin, vascular engorgement, plugged meibomian gland orifices, anterior or posterior replacement of mucocutaneous junction), and poor meibum expression under digital pressure.⁴¹ The severity of MGD was graded by meibography using Keratograph 5 M[®] (Oculus, Wetzlar, Germany) to generate a meiboscore

by combining the scores for the upper and lower eyelids as previously reported⁴²: 0, no meibomian gland loss; 1–2, mild, less than one-third total gland loss; 3–4, moderate, one-third to two-thirds total gland loss; and 5–6, severe, more than two-thirds total gland loss.

The study showed that symptomatic MGD was significantly more prevalent in the study group (54/60, 90%, Figure 3) than in the control group (29/45, 64%, $P=0.001$). Furthermore, moderate and severe MGD, i.e. more than one-third meibomian gland loss, was noted in more than half of the study group (35/60, 58.4%), but only one patient in the control group (1/45, 2.2%, $P<0.001$). Accordingly, the meiboscore in the study group was significantly higher than that in the control group, regardless of whether the data were analyzed as a whole group (3.3 ± 2.1 vs. 0.9 ± 0.4) or a subset of MGD patients (3.6 ± 1.9 vs. 1.2 ± 0.8) in each group (both $P<0.001$). Intriguingly, MGD was worse in the upper eyelid of the study patients (meiboscore upper vs. lower: 2.1 ± 1.0 vs. 1.5 ± 1.1 , $P<0.001$, $n=45$), but similar between the upper and lower eyelids of the control patients (meiboscore upper vs. lower: 0.5 ± 0.5 vs. 0.7 ± 0.5 , $P=0.1$, $n=29$). Superficial punctate keratopathy was detected in 15 of 60 study patients (49.1%), being significantly more prevalent than the 4 of 45 patients (36.9%) in the control group ($P=0.03$).

The study patients with MGD had a significantly higher Schirmer I values (8.8 ± 3.3 vs. 6.3 ± 1.9 mm/5 min, $P=0.048$) than the control patients, although both groups had comparably short break-up time (2.5 ± 1.3 vs. 3.2 ± 1.1 s, $P=0.07$). The higher tear secretion may be explained by increased reflex tears from the ocular surface inflammation associated with demodicosis. Besides MGD, the study patients had more eyelash abnormalities (85% vs. 4.4%, $P<0.001$) and more blepharitis (78.3% vs. 4.4%, $P<0.001$) than the control patients.

Collectively, these findings suggest that ocular demodicosis may be a potential cause of MGD and further disturbance of the tear film.⁴ We were surprised to see such severe meibomian gland loss in such a young population. It will be important to follow-up these young patients for a longer time period to observe whether the MGD deteriorates over time. We also wonder whether the MGD normally found in older populations may have a root cause in early insidious, but cumulative, demodicosis at a younger age.

OCULAR DEMODICOSIS AND KERATITIS

For the first time, Kheirkhah et al.¹⁶ reported demodicosis-related corneal changes, including superficial corneal vascularization, marginal corneal infiltration, superficial corneal opacity, nodular corneal scar, and phlyctenule-like lesions in 6 cases. Surprisingly, and contradicting the notion that *D. folliculorum* is much more commonly found than *D. brevis*, *D. brevis* was detected in 3 of their 6 cases.

Recently, we detected *Demodex* infestation in 15 cases with refractory and recurrent keratitis, and successfully treated these cases by killing the mites. The corneal findings included peripheral stromal infiltration with neovascularization in 16 eyes (Figure 4), superficial punctate keratopathy in four eyes, central stromal infiltration in two eyes, limbitis in two eyes, and perforation in one eye. The keratitis was more commonly bilateral (67%)

than unilateral (33%), and 13 of 15 patients (86.7%) were accompanied with predominant blepharitis. All of these keratitis cases had previously been diagnosed as herpes keratitis, but failed to respond to antiviral therapies including topical and systemic ganciclovir treatment. After killing the mites by eyelid cleaning with Cliradex[®] (Bio-Tissue Inc., Miami, FL), the active keratitis resolved within 1 week. This quick response to the mite-killing therapy implies an immune response mechanism, because it usually takes 6–8 weeks to fully eradicate mites, although terpinen-4-ol, an active ingredient of Cliradex[®], has an anti-inflammatory effect. This notion is further supported by our unpublished observation that predominant Langerhans cell infiltration in the corneal foci was detected by confocal microscopy. Consistent with the findings of Kheirkhah et al.,¹⁶ the prevalence (14/15 vs. 13/15) and mean counts (3.2 ± 1.6 vs. 2.9 ± 2.1) of *D. folliculorum* and *D. brevis* were comparable (both $P > 0.5$) in the patients. These findings again suggest that *D. brevis* may have a higher potential for triggering corneal changes.

The recurrence history and slit-lamp appearance of demodicosis-related keratitis are similar to herpes virus keratitis. However, the association with blepharitis, response to mite-killing therapy, and eyelash sampling can help to confirm the correct diagnosis.

DIAGNOSIS

The diagnosis of demodicosis is mainly based on clinical evaluation and confirmed by microscopic detection of *Demodex* mites in epilated eyelashes. Thus, the clinical diagnosis is imprecise. Symptoms such as blepharitis, blepharoconjunctivitis, ocular rosacea, eyelash disorders, and chalazia may be suspicious for *Demodex* infestation. CD is a reliable diagnostic sign.²³ Under slit-lamp examination, CD has the appearance of solidified exudative excretions around the base of the eyelashes.

Demodex detection can be easily performed by ophthalmologists or technicians. Briefly, two eyelashes with CD per eyelid are removed with fine forceps under a slit lamp. Sampling of eyelashes with CD is more likely to yield good results than random epilation.⁴³ Under a light microscope, one drop of saline is applied with a pipette to the edge of the coverslip before examination. For those with retained CD, adding one drop of fluorescein solution, peanut oil, or 75% alcohol can help the embedded *Demodex* to migrate out. The biggest question is the cut-off number of mites detected. As *Demodex* mites can be found in asymptomatic populations, it remains unclear how many eyelashes should be sampled and how many mites are capable of inducing pathologic changes.

Recently, *in vivo* confocal laser scanning microscopy (CLSM) has been used to detect *Demodex* infestation.⁴⁴ *Demodex* mites present as roundish or lengthy cone-shaped structures under CLSM. However, it is difficult to distinguish the two types of *Demodex* mites under CLSM in most cases. In addition, cooperation of the patient is highly required.

Diagnosis of demodicosis in children is challenging, if not problematic, because of their poor cooperation during epilation. CD in children is not as obvious as that in adults. Furthermore, the *Demodex* count in children tends to be lower than that in adult patients,²³ presumably because of the relatively shorter infestation period. Therefore, sampling of a

much higher number of eyelashes in children than advised in adults may be warranted to establish the diagnosis of ocular demodicosis, especially when CD is not apparent. However, given that demodicosis is thought to be nil or very rare in the normal pediatric population,²⁹ detection of any number of mites is significant.

TREATMENT

Demodex mites are resistant to a wide range of antiseptic agents, including 75% alcohol, 10% povidone-iodine, and erythromycin.¹² By *in vitro* microscopic observation for 150 min, Gao et al.¹² found that *D. folliculorum* can be dose-dependently killed by TTO. TTO not only cleanses CD from the eyelash roots, but also stimulates the embedded mites to migrate out to the skin. Apart from *Demodex* eradication, TTO exerts actions that are antibacterial,⁴⁵ antifungal,⁴⁶ and anti-inflammatory.⁴⁷

Patients with ocular demodicosis are instructed to use Cliradex[®], which contains TTO as an active component, as an eyelid scrub twice daily for 3 months to eradicate *Demodex* mites. Specifically, after washing the face and eyelids with baby shampoo or soap and rinsing with warm water, Cliradex[®] is smeared onto the eyelash roots at both the upper and lower eyelid margins with the eyes closed.

In summary, *Demodex* mites are the most common microscopic ectoparasites found in the human skin and eye. *Demodex* infestation is often overlooked in clinical investigations of ocular surface inflammatory diseases and may be a cause of antibacterial and antiviral treatment failure. Although its pathogenesis has been debated for a long time, increasing evidence suggests that *Demodex* infestation is a potential cause of ocular surface inflammation in blepharitis, blepharoconjunctivitis, MGD, pterygium, chalazia, eyelid basal cell carcinoma, and sight-threatening keratitis.

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Figure 1.

Microscopic features of *D. folliculorum* (A) and *D. brevis* (B). These obligate mites are transparent, elongated in shape, and divided into head-neck and body-tail parts, with eight short legs attached to the former body segment. The head-body ratio is 1:2 to 1:4 for *D. folliculorum*, but close to 1:1 for *D. brevis*.

Figure 2.

Slit-lamp photographs of a case with demodicosis and blepharoconjunctivitis. A 23-year-old female presented with itching in both eyes for 6 years. Four *D. folliculorum* mites were detected by eyelash sampling. Cylindrical dandruff (CD) was present around the eyelash roots (A, B). Follicular reaction was predominant (B). After a TTO eyelid scrub, with reduction in the *Demodex* count, the symptoms were relieved and the CD and the conjunctival follicles disappeared (C, D).

Figure 3.

A case with ocular demodicosis and MGD. A 16-year-old female complained of irritation and dryness in both eyes for 4 years. She also had a past history of chalazia in both eyes. Two *D. folliculorum* and two *D. brevis* mites were detected. Slit-lamp examination revealed irregular, thickened, and inflamed eyelid margins and conjunctival injection in both eyes (A, B). Meibography showed meibomian gland dropout in both eyes (C, D).

Figure 4.

A case with ocular demodicosis and corneal ulcer. An 18-year-old female complained of recurrent redness and irritation in her left eye for 9 years. Two years previously, she underwent penetrating keratoplasty in the left eye for corneal perforation caused by presumed herpes simplex keratitis. Two months previously, the keratitis recurred in the left eye, but failed to respond to antiviral and antibiotic regimens. Examination revealed blepharitis (A) and corneal stromal infiltration with epithelial defect and neovascularization (B). Eyelash sampling revealed two *D. brevis* and two *D. folliculorum* mites. After performing eyelid scrubs with Cliradex[®] for 6 days, the ocular surface inflammation was significantly reduced (C) with healing of the corneal ulcer (D).