What’s all the craze about demodex?

A alleviate confusion on prevalence, morbidity, and treatment

March 23, 2016
By Ben Gaddie, OD, FAAO

While many eyecare practitioners (ECPs) are just now learning about demodex infestation of the eyelids and adnexa, the fact is that this condition has been around for as long as mankind. The entomologists Johannsen and Riley from Cornell University first described the species in detail anatomically as early as 1915, but it wasn’t until the 1960s that clinical reports of demodex-related blepharitis began to emerge in the literature.

Yet this common condition largely flew under the radar in terms of clinical recognition despite its ubiquitous nature and nebulous but certain contributor to ocular surface inflammation and disease. The craze of ECPs diagnosing and treating demodex-related blepharitis has a lot of “craze” to it—there are many misperceptions out there from prevalence to morbidity, treatment, and beyond. Here, we will review the current thinking around this hysterical phenomenon.

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Two types of Demodex

Demodex mites are microscopic ectoparasites found in human skin. They are extremely common, and their rate of infestation increases with age. The life span of demodex outside the living body is very limited. Direct contact is thought to be required for transmission of the mites. The lifecycle of demodex from egg/molt to an adult is quite short and no longer than two to three weeks. The adult stage is less than a week, and this is when mating occurs.
There has been much discussion about the means of mating for demodex, from mass reproduction on the host eyelid during sleep to microscopic size differences in genitalia. The fact is, demodex are proficient and efficient at reproducing. What it isn't well understood is why so many people don't have symptoms of obvious clinical demodex.

There are two species: Demodex folliculorum and Demodex brevis. D. folliculorum involves infestation of the hair follicles, most commonly the eyelash follicle. This type can also be found in adnexal infestations involving the small hair follicles around the eye and face. Anatomically, D. folliculorum is longer and thinner than its brother D. brevis.

D. brevis prefers sebaceous glands of the face as well as the meibomian glands. Sebum (and presumably meibum) is the main food source for the brevis variety. D. brevis has been implicated as a causative factor in several subtypes of rosacea. Indeed, rosacea affects the same sebaceous glands that brevis like so well. Demodex have been implicated as the cause of many other dermatological conditions including perioral dermatitis.

**Demodex and ocular involvement**

Demodex can have a range of effects on the eyelid, adnexa, and ocular surface, including the cornea. Demodex-related blepharitis could be classified as anterior or posterior blepharitis. Anterior blepharitis is considered an infestation of the eyelashes and follicles primarily by D. folliculorum, whereas posterior blepharitis includes infestation of the meibomian glands with D. brevis mites. Around the lash follicle, demodex mite claws can induce chronic inflammation, leading to distention of the follicle and the formation of cylindrical dandruff. In posterior blepharitis, D. brevis mites can obstruct meibomian gland orifices leading to meibomian gland dysfunction (MGD), hordeolum, and chalazia. Inflammation results from both types of demodex blepharitis.

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Tseng and colleagues have recently demonstrated the formation of pro-inflammatory proteins produced by living and dying demodex that may be responsible for initiating the host inflammatory response. **This inflammatory response sets up a cycle of MGD and rosacea.** In addition, Tseng also recently demonstrated an association between ocular demodex infestation and immunoreactivity to Bacillus in patients with facial rosacea.

**Other eyelash-related manifestations of demodex infestation include MGD, lid margin inflammation, and redness.** Mechanical blockage of the meibomian gland by D. brevis mites can lead to obstruction, inflammation, and gland atrophy, often indistinguishable from otherwise capped or plugged glands associated with MGD. **Lid margin inflammation is associated with facial rosacea, which is associated with demodex.**

Other anterior segment manifestations originate from the lid margin and meibomian glands, where the inflammation can progress to the conjunctiva and cornea. One of the most common acute or subacute clinical condition we see is blepharoconjunctivitis, which means inflammation (and infection) of the lid and conjunctiva. Most patients are responsive to a topical
antibiotic/steroid combination, but those refractory from topical therapy are often misdiagnosed and must be considered for demodex involvement. Other commonly misdiagnosed causes likely attributable to demodex include corneal marginal infiltrative keratitis, phylctenules, nodular scarring, and corneal neovascularization.\textsuperscript{9}

**Diagnosing demodex**

Clinical history is an important facet of diagnosing demodex and is helpful in determining which patients should be treated. Any anterior segment disease such as blepharitis, hordeolum/chalazia, or conjunctivitis that is recurrent and not resolved with topical therapeutic agents should be suspected of a demodex problem.

Lash loss or focal lash loss should be noted. Chronic watering, presumably as a result of reflex tearing in evaporative dry eye associated with MGD, is a common complaint from patients suffering from demodex infestation. Patients with a history of allergic conjunctivitis should be questioned about the location of the itching. Responses indicating eyelid margin itching are suspects for demodex. Facial and eyebrow itching are also suspect responses.

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Diagnosis can be made clinically or microscopically by observing cylindrical dandruff or epilating lashes for microscope detection of mites. While it is tempting to demonstrate microscope evidence to patients, the process of epilating and examining for live demodex is time consuming and in my opinion unnecessary in the vast majority of cases in order to make a diagnosis. Furthermore, the psychological distress of seeing living critters on a patient’s eyelids is sometimes too much for the patient and results in delusions and paranoia.

Simple clinical slit-lamp examination of the lightly closed upper eyelids will demonstrate evidence of frank clear to waxy cylindrical dandruff on the base of the lash line. Cylindrical dandruff is pathognomonic for demodex.\textsuperscript{10} Infrequently, cylindrical dandruff is not visible, but dandruff like flecks can be seen around the base of the lash on examination. There are cases of demodex in which there is no detectable dandruff because the evidence of demodex is hidden. Mastrota recently published about her technique of mechanical eyelash rotation to mechanically discharge the dead mites and their waste, revealing evidence of the tails of demodex.\textsuperscript{11}

**Treating demodex**

As was mentioned, this condition is so highly prevalent that it could be treated en mass. The dilemma with this condition is deciding which patients should be treated or even told of their condition. When patients are symptomatic, it is pretty easy to justify treatment. The challenge is identifying symptoms that could be attributed to diseases such as allergic conjunctivitis or inflammatory dry eye that are really a manifestation of demodex.

The mainstay and only effective treatment of demodex is tea tree oil (TTO), which contains 4-Terpinenol.\textsuperscript{12} It’s interesting to consider the onslaught of shampoos and cosmetic products
containing TTO in the last few years. When you consider the association among demodex, rosacea, MGD, and seborrhea, it’s easy to see why they may be on to something.

TTO is toxic to demodex in a dose/response manner. However, higher concentrations are associated with increased irritation. The goal in formulating commercially available TTO-containing products is to make them strong enough to eradicate the mite or be toxic enough to interrupt the reproductive cycle without irritating the skin or eyes. After treating demodex for years now, clearly my goal is to control the demodex population on my patients as gently as possible to alleviate symptoms. Expectations to eradicate demodex clinically in patients are unrealistic, if not impossible.

Related: Diagnosing demodex

Once the decision has been made to treat a patient, the doctor must decide between in-office treatment vs. at-home treatments. Several companies, including OCU SOFT, Bio-Tissue, and Macular Health offer doctor-directed in-office treatment of demodex. The TTO concentration for in-office application is significantly higher than the concentration contained in the pads. Clinical tip if you decide to treat in office: utilize the BlephEx brush to loosen the cylindrical dandruff and other biofilms on the lid surface. This will allow for greater penetration into the follicle where the mites are hiding out. We found in our practice that the time, odor, and patient discomfort of in-office treatment didn’t seem worth the effort when I compared patients’ symptomatic improvement to those who were self-treated with commercial TTO lid scrubs. I felt like while our in-office patients had fewer demodex counts microscopically after a month, our at-home patients had equal or better symptomatic improvement.

The at-home TTO-containing therapies come mostly in either pre-medicated individually sealed pads or in a multi-dose foam bottle dispenser. The most commonly used and generally effective brands include Cliradex (Bio-Tissue), Blephadex (Macular Health), and Oust Demodex Cleanser (OCU SOFT). I have found these formulations to be effective in reducing symptoms and improving overall lid margin appearance. However, there is a difference in the tolerability of the treatments. In my experience, Blephadex has the least amount of burning and stinging, followed by Oust, then Cliradex. This likely has to do with the relative percentages of TTO in the formulations. These therapies are now part of our standard post LipiFlow (TearScience) supportive therapy. Given the association among demodex, rosacea, and MGD, it makes sense to keep demodex away from freshly treated meibomian glands.

In summary, ocular demodex is a very common condition that can range from asymptomatic to sight-threatening disease. Demodex has now been associated with facial and ocular rosacea as well as MGD. Quick recognition and diagnosis and conservative at-home treatment will lower the mite density and interrupt their reproductive cycle enough to bring about symptomatic improvement. Most patients will require ongoing daily hygiene and periodic aggressive therapy to control ocular demodex.
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Ben Gaddie, OD, FAAO
Dr. Gaddie is the owner and director of Gaddie Eye Centers, a multi-location, full-service practice in Louisville, KY. He is a Fellow of ...

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Factors in rosacea pathogenesis clearer

January 01, 2017
By John Jesitus

Monterey and Newport Beach, Calif. – For every rosacea-related question that research answers, according to experts at recent meetings, several unsolved issues remain. However, they agree that reducing rosacea symptoms begins with teaching patients to avoid triggers.

Many moving parts

The difficulties in understanding rosacea stem from its multiple forms (erythematotelangiectatic/ETT, papulopustular/PP, phymatous and ocular) and potential mechanisms (vascular, innate immune, neurological and diet), said Guy F. Webster, M.D. He is a Hockessin, Del.-based dermatologist and past president of the American Acne & Rosacea Society (AARS).

Nevertheless, said AARS president-elect Julie C. Harper, M.D., "It's important that dermatologists have some understanding of what we're learning about the pathogenesis of rosacea. We must know where in that pathway our treatments potentially work." She is a Birmingham, Ala.-based dermatologist in private practice who is affiliated with the University of Alabama at Birmingham.

Conceptually, Dr. Webster advanced two potential models for rosacea pathogenesis, the first involving multiple, perhaps equally culpable, cofactors such as histamine, cathelicidins and the innate immune system. "If any of them are out of balance, that can get the rosacea gears turning."

Dr. Harper said, "We believe that some of the normal innate immune pathways are working overtime in people with rosacea. There's too much toll-like receptor (TLR)-2 activity, cathelicidin activity and kallikrein 5, which turns the inactive form of cathelicidin into LL37, the antimicrobial peptide at work in rosacea." Mouse models and ex vivo human skin studies have shown that LL37 increases skin symptoms such as erythema and telangiectasias, she said.

Within the innate immune system, mast cells may represent a promising target. Dr. Webster explained, "Mast cells communicate with nerves. And one of the things we know for sure about rosacea is that the nerves trigger blood vessel functions including vasodilation and constriction. The mast cell may well be at the heart of rosacea - if one can calm it down, rosacea also may calm down, in theory."
Alternatively, he said, "One might say that there is one prime driver – I’d conjecture that it may be a neurological stimulus – and all the other factors are epiphenomena."

Triggers such as heat, stress and spices stimulate the transient receptor potential vanilloid (TRPV 1 through 4) and transient receptor potential ankyrin (TRPA) channels. These receptors play a role in inflammation and innate immunity, Dr. Harper said. Along with cardiovascular disease, recent research suggests epidemiologic links between rosacea and Parkinson's disease, glioma and autoimmune diseases. While epidemiologic associations do not establish causality, she said, researchers began investigating in these directions because these illnesses share common inflammatory pathways.

Clinically, said Dr. Harper, "We see flushing, stinging, and papules and pustules. We also know what the triggers are - our patients tell us what makes their rosacea worse. It's different for different people. But the most common one is usually ultraviolet light."

Edible triggers such as chocolate, cheese and red wine share a common feature: fermentation, said Dr. Webster. This process can deaminate histidine, creating histamine, which has many vasoactive properties, such as inducing blush and itch, he said. "Nobody has shown that histamine in food turns on rosacea." The concept may have merit, he said, though presently it remains conjecture.

Conversely, Dr. Webster said, some forms of niacin may dilate blood vessels. If a rosacea-prone person takes niacin that's released all at once (versus delayed-release), he explained, the person gets a hot flash – which can set off rosacea – when it's absorbed.

Pathological subtleties aside, said Dr. Harper, patient education remains crucial. "We can write all these prescriptions, but it is still very important that we educate our patients about rosacea triggers." Complete avoidance is rarely possible. "But if we can lessen exposure to those triggers, we have the ability potentially to lessen the impact of innate immunity and the neurological dysregulation."

Unfinished business

The impact of other potential pathogens remains unsettled. For example, said Dr. Webster, European physicians accept completely that the Demodex folliculorum mite is the root of rosacea. "If you ask me, or many American dermatologists, it's less decided." Although D. folliculorum levels are elevated in rosacea, he explained, people can have heavy D. folliculorum colonization, but no rosacea, and vice versa. The fact that Demodex levels are highest in ETT rosacea counters the assumption that mites attack the hair follicles, causing inflammation and pimple formation, he added.

"The issue is confounded by the fact that the anti-mite drug Soolantra (topical ivermectin, Galderma) works well in rosacea. But no one has fulfilled Koch's postulates: by showing that killing the Demodex improves rosacea; that Soolantra lowers Demodex levels; and that patients who resist Soolantra have Demodex levels that don't decrease with treatment." One cannot assume that topical ivermectin works in rosacea by killing Demodex, he said, because antibiotics
such as doxycycline work in rosacea through many non-antibiotic effects. Topical ivermectin also has anti-inflammatory activity, he noted.

Also unclear, he said, is the contribution of Bacillus oleronius. This bacterium has been found to have antigens (chaperonin GroEL and aconitate hydratase) that excited the lymphocytes of patients with rosacea, but not in normal subjects. "It sounds like something's going on there. Also, the immune response to B. oleronius was found to be especially elevated in ocular rosacea. But we don't know that the antigens in this bug are unique to this bug. Much remains to be worked out. It's a stretch to conclude that the bug isolated from one mite of 40 studied is relevant. I'd be more convinced if these antigens are in Propionibacterium acnes or some known skin resident" that causes disease.

Answers to the above conundra may come slowly, Dr. Webster cautioned. With few dermatologists directly researching rosacea mechanisms, he said, insights regarding rosacea frequently emerge from other research, often in neuroimmunology.

Dr. Harper added, "We must give Richard Gallo, M.D., Ph.D., a lot of credit. He's done much of the research in rosacea." He is professor and chief of dermatology at the University of California, San Diego.

Annually, the AARS offers grants to spur research in rosacea and acne. Dr. Harper said, "We have multiple grants that will be available in 2017. We would love to have any dermatologist or other researcher interested in furthering the understanding of rosacea apply."

Disclosures: Dr. Webster has been a consultant, researcher and/or advisor for Allergan, Dermira, Galderma, Valeant, Sienna, BiopharmX, Sol-Gel, Foamix, Almirall, Cutanea and Sun Pharmaceutical Industries Ltd. Dr. Harper has been a consultant, researcher and/or advisor for Allergan, Bayer, Galderma and Promius Pharma. This article is based on presentations given by Dr. Webster at the Coastal Dermatology Symposium, Monterey, Calif., and by Dr. Harper at the Skin Disease Education Foundation (SDEF)'s 12th Annual Women's & Pediatric Dermatology Symposium, Newport Beach, Calif.

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