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EDITORIAL

The impact of ocular demodicosis on the eyes

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Demodex is a commonly overlooked contributor in ocular surface inflammatory diseases. Demodex infestation ranges from 29% to 91% across a variety of geographic locations and study populations [1]. Ocular demodicosis increases with age, and is associated with eyelid disorders including anterior blepharitis, meibomian gland dysfunction (MGD), chalazia, and blepharo-keratoconjunctivitis in both adult and pediatric populations [2, 3]. Tear film instability [4, 5], pterygium recurrence [6], and rosacea have been linked to Demodex. Blepharitis was the first reported to be associated with ocular demodicosis in 1959 [7].

Two distinct species of *Demodex*, have been identified in humans. *Demodex folliculorum* is more strongly associated with anterior blepharitis while *Demodex brevis* with MGD, recurrent chalazia, and refractory keratitis [2, 8]. Demodex may reside as normal flora in healthy or asymptomatic diseased individuals [1, 4] but become pathogenic when organism numbers reach a critical threshold, which are then sufficient to induce or exacerbate ocular symptoms. Higher numbers of Demodex have been noted in Demodex blepharitis (DB) compared to controls [2], however, the minimum number of Demodex required to induce symptoms remains unknown. Impaired immunity may contribute to the necessity of a threshold number of organisms needed to trigger a host response. Systemic factors that may impair the immune system, such as obesity, smoking, malignancy, diabetes mellitus, and acquired immunodeficiency syndrome, have been identified as risk factors for Demodex infestation. Animal models for Demodex induced disease are currently unavailable as humans are the only hosts.

Many questions remain unanswered, including why there is poor correlation between symptoms and objective signs of DB. In this issue of *Eye*, experts on the Demodex Expert Panel on Treatment and Eyelid Health (DEPTH) panel attempt to achieve consensus regarding the symptoms and diagnosis of DB [9]. Consensus was reached on several points. *First*, careful examination for signs of DB is an integral part of a routine ocular exam. *Second*, itching is the most common presenting symptom of Demodex infestation. Itching is more frequently reported in individuals with Demodex compared to individuals without Demodex in a number of ocular diseases [10] including blepharitis [11], dry eye disease [5], and controls [12]. Higher Demodex numbers have been associated with a higher degree of itching [5, 13]. Itch sensation is transmitted by both histaminergic (acute itch), and nonhistaminergic (chronic itch) pathways. It is the latter pathway that has been linked to DB [14]. High level of IL-17 [14], one of the nonhistaminergic pruritogens, was reported in individuals with Demodex. Study has also shown that the treatment of Demodex leads to improvement in individuals with refractory itch sensation [13].

Third, cylindrical dandruff (CD) is the most common and pathognomonic finding in individuals with DB. This association was documented as early as 1963 in an individual with severe blepharitis and numerous Demodex identified via microscopic examination [15]. CD was described as "an accumulation of debris at the free margin of the eyelids" and the authors recommended including CD as a clinical feature of Demodex. With regards to terminology, "collarettes" was agreed upon as the consensual term for CD. "Collarettes" has been found to be the ocular sign most closely related to DB. However, it is important to note that the term "collarettes" is not specific to DB. This term has been described repeatedly in Staphylococcus related diseases, with Demodex collarettes presenting as gelatinous scales collaring the lash root [16] and Staphylococcus related collarettes as greasy scales located away from the lash root.

Different theories explain why DB might present with collarettes at the lash root. Collarettes may represent a human immune response against bacteria *(Bacillus oleronius)* carried on Demodex. This hypothesis is supported by in vitro studies showing that when the produced *Bacillus oleronius* protein was added to human serum, an inflammatory response was noted with increased neutrophil migration and release of inflammatory cytokines [17, 18]. Another hypothesis is that *Demodex folliculorum* mechanically irritates the epithelium of the hair follicles, inducing epithelial hyperplasia and reactive hyperkeratinisation that presents as collarettes. Histopathologic study of biopsied eyelid tissues has reported that *Demodex folliculorum* was strongly associated with hyperkeratinisation, and perifollicular inflammation [19]. The chitinous exoskeleton of *Demodex brevis* is thought to act as a foreign body, causing deeper granulomatous reactions when it burrows deep into the meibomian glands. However, when *Demodex brevis* migrates to the surface, the inflammatory cicatrix may present as a collarette [20]. Finally, collarettes may represent a polysaccharide biofilm produced by Staphylococcus aureus and epidermidis. This biofilm may provide an armor that host defenses such as white blood cells, antibiotics, povidone-iodine scrubs cannot penetrate and furthermore, provide a food source for Demodex [21]. While all of these theories are biologically plausible, a lack of molecular studies limits the ability to definitively point to the source of Demodex collarettes.

Fourth, DB is associated with an abnormally rapid tear break up time (TBUT). The panel concluded this despite previous studies showing inconsistent relationships between Demodex presence, ocular surface symptoms, and tear parameters [22]. This issue is important because it points to an overlap between signs of Demodex, aqueous tear deficiency, and other sub-types of dry eye disease (DED). It also reaffirms the importance of evaluating for symptoms and signs beyond tear parameters (e.g., itching and collarettes), as this can guide the physician toward considering Demodex as a contributor to tear instability [5].

The gold standard for diagnosing DB is eyelash epilation and observation of the organism under light microscopy. In vivo laser confocal microscopy (IVCM) can be an alternative for visualization. However, the high reflectivity of substantia propria and potential misinterpretation remain challenging. As microscopy is often impractical to perform in the routine clinical setting, the panel concluded that the diagnosis of DB can be made based on the slit lamp observation of pathognomonic collarettes alone.

The causative association between Demodex and blepharitis in asymptomatic patients has not been established. There is also

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insufficient evidence to establish the threshold number of Demodex organisms required to induce symptoms. Panelists agreed that an increase in the number of Demodex organisms (as determined by lash sampling) was associated with pathogenic activity, collarette severity, and symptoms. As such, serial Demodex counts can be used as an objective measurement to monitor treatment efficacy. The goal of treatment is to reduce Demodex counts, alleviate clinical signs of disease, and improve symptoms. The panel agreed that treatment is indicated in the setting of collarettes with symptomatic blepharitis, but no consensus was achieved as to the most effective treatment. A meta-analysis reported comparable efficacy with local and systemic treatments, including tea tree oil (TTO), terpinen-4-ol (T4O, an active component of TTO), pilocarpine gel, ivermectin, and metronidazole, for DB [23].

Demodex should be considered in the presence of anterior blepharitis, keratitis, chalazia, or DED that is unresponsive to conventional treatments. In addition, Demodex is found more prevalent and complicates the clinical course of patients with chronic severe rosacea by stimulating the inflammatory process. Their coexistence and potential to exacerbate each other makes the diagnosis and treatment challenging. Recent studies showed that eradicating Demodex can also lead to resolution of chronic severe rosacea cases [24, 25], similar to that of DB. More research is needed to understand Demodex pathogenicity and its association with ocular diseases, including in vitro, ex vivo, and clinical trials. Specifically, there is a need to study relationships between Demodex and the immune system which may lead to the identification of new therapeutic targets.

Anny Mansim Cheng[1,2,3]✉, Anat Galor[4,5], Raphael Banoub[1,2] and Shailesh K. Gupta[1,2]

[1]*Department of Ophthalmology, Broward Health, Fort Lauderdale, FL, USA.* [2]*Specialty Retina Center, Coral Springs, FL, USA.* [3]*Department of Ophthalmology, Florida International University, Herbert Wertheim College of Medicine, Miami, FL, USA.* [4]*Department of Ophthalmology, Miami Veterans Administration Medical Center, Miami, FL, USA.* [5]*Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami, Miami, FL, USA.*

✉*email: acheng@browardhealth.org*

DATA AVAILABILITY

All data generated or analyzed during this study are included in the published article [9].

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AUTHOR CONTRIBUTIONS

AC was responsible for designing the review protocol, writing the manuscript, extracting and analyzing data, interpreting results, and updating reference lists. AG contributed to writing the manuscript, interpreting results, review and provided feedback on the manuscript. RB contributed to the writing the manuscript and updating reference lists. SG contributed to writing the manuscript, interpreting results, review and provided feedback on the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Anny Mansim Cheng.

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