

## Research Article

# Chronic Blepharitis due to *Demodex*: A Prospective Study in Sfax (Tunisia)

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## Keywords

- *Demodex*
- Chronic blepharitis
- Eye irritation
- Dryness

## Abstract

**Introduction:** Chronic blepharitis is a common cause of eye irritation and dryness. They are often treated without regard to causal factors such as parasites which are rarely mentioned.

**Purpose of Work:** The aim of this study is to describe the role of *Demodex* in the pathogenesis of chronic blepharitis, to analyze the epidemiological, clinical, diagnostic and therapeutic particularities and to propose a therapeutic approach.

**Methods:** This is a prospective, case-control study conducted in the mycology parasitology department at the Habib Bourguiba university hospital in Sfax over a 12-month period from October 2015 to October 2016, covering 100 cases with chronic blepharitis and 87 control cases.

Clinical examination and eyelash removal were performed with direct examination for qualitative and quantitative analysis, before and after treatment.

**Results:** *Demodex* was significantly more found in patients than in controls (48% vs 13.8%). Similarly, the quantitative analysis showed a significant difference between the two groups with 52.1% of *Demodex* (+++) for patients versus 8.3% for controls.

The cases with *Demodex* blepharitis were treated with mercuric oxide (yellow) ophthalmic ointment with a good outcome in 81,3%.

**Conclusion:** Although it is admitted to be a saprophyte of the skin, a large number of arguments argues for the incrimination of *Demodex* in the etiopathogenesis of chronic blepharitis, hence the interest of eyelashes examination and a parasitic research in front of any chronic blepharitis resistant to usual treatments. In case of positive research, a specific treatment should be prescribed. Its effectiveness is another argument for the etiological diagnosis.

Although it is admitted to be a saprophyte of the skin, *Demodex* seem to be accused in the genesis of the chronic blepharitis.

## INTRODUCTION

Blepharitis is a common ophthalmic disease resulting in acute or chronic inflammation of the free margin of the eyelids. We distinguish the anterior forms, mainly affecting the skin covering, the posterior forms, affecting the meibomian glands and mixed affecting both sides. Clinically, erythematous, crusted, ulcerative and scaly blepharitis is distinguished.

Chronic blepharitis frequently poses diagnostic and therapeutic problems. Indeed, a wide variety of etiological factors have been put forward. Among these etiologies, the parasitic origin (*Demodex*) is rarely implicated, leading in some cases to avoidable therapeutic failures.

The etiological diagnosis of chronic blepharitis is necessary in order to adapt the treatment and avoid recurrences. The aim of this study was to determine the pathogenic role of parasites (*Demodex*) in the genesis of chronic blepharitis while analyzing the epidemiological and clinical particularities of our patients,

and to propose appropriate management in the face of chronic blepharitis resistant to the usual treatment.

## PATIENTS AND METHODS

This was a prospective, case-control study, carried out at the Habib Bourguiba University Hospital Center in Sfax within the parasitology-mycology laboratory, over a period of 12 months. It interested a group of 100 patients with chronic blepharitis and a group of 87 controls.

For each patient, an information sheet was completed specifying age, sex, occupation, ophthalmic history and other history such as diabetes, history of the disease, functional and physical ophthalmic signs.

Each patient received a sample of three to five eyelashes from each eye alternating between the upper and lower eyelid using tweezers. The samples were taken without any local treatment.

Cilia and adjacent debris were quickly observed in a drop of 30% KOH potash between slide and coverslip under the

microscope at objective 10 to confirm the presence of Demodex then 40 for parasitological identification. A semi-quantification in number of crosses was made for all the positive samples. Demodex (+++) corresponds to a pullulation of 3 Demodex and more, (++) corresponds to the presence of 1 to 3 Demodex. But it is a reading that remains subjective.

For our patients, the inclusion criteria were chronic and/or recurrent blepharitis (more than 6 months) with no improvement under usual local treatment (antibiotic, antiseptic and eyelid hygiene). The exclusion criteria were acute or focal isolated blepharitis such as stye and chalazion.

We randomly selected 87 control cases. Exclusion criteria were history of blepharitis and/or abnormal eyelid examination, history or signs of seborrheic dermatitis, rosacea or pityriasis versicolor and wearing contact lenses or instillation of eye drops in the seven days preceding the collection.

Faced with chronic blepharitis with a positive Demodex direct examination, an ointment of yellow mercury oxide was prescribed for application at the base of the eyelashes once a day, preferably in the evening for 15 days, in the case of Demodex (+) and for one month in the case of Demodex (+++), preceded by rigorous daily eyelid hygiene.

Statistical analysis of the data was performed using IBM SPSS Data Editor software. Comparisons between the results of our two groups were made using the Chi2 test. A p value <0.05 was considered statistically significant.

## RESULTS

### Sick group

They were 67 women and 33 men with a sex ratio of 0.49. The average age was 49.13 years ( $\pm 17.78$ ) with extremes ranging from 9 to 79 years. The most affected age group was between 51 and 60 years old with 26% of patients. Demodex prevalence increased with patient age. Indeed, it is higher in elderly subjects (61-80 years old) reaching 71.4% in comparison with younger subjects (21-40 years old) with only 21.4%. This difference was significant ( $p=0.001$ ).

The clinical signs leading the patient to consult were pruritus (50%) or ocular burning (28%), sometimes paradoxical tearing (16%).

Blepharitis was scaly and/or erythematous in the majority of cases (87 patients) (Figure 1,2,3).

A tubular clear sleeve around the eyelashes was quite characteristic of Demodex blepharitis (Figure 4,5).

We found 28 patients with meibomian gland dysfunction (MGD). The frequency of MGD increased with the population of Demodex in the cilia. Indeed, MGD was present in 21.2% of cases in the absence of Demodex, in 30.4% of cases with Demodex (++) and in 40% of cases with Demodex (+++) ( $p=0.216$ ) (Figure 6).



Figure 1 Chronic erythematous blepharitis.



Figure 2 Chronic scaly blepharitis.



Figure 3 Chronic crusty blepharitis.

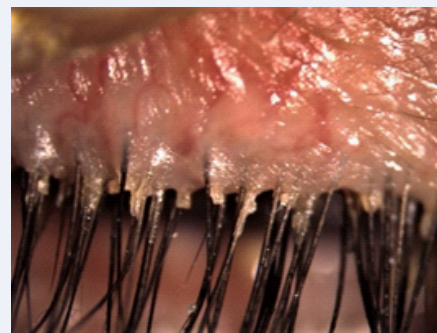


Figure 4 Squamous Blepharitis with Demodex with sleeves.

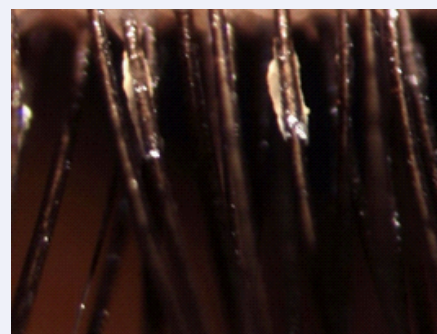


Figure 5 Clear tubular sleeves around the eyelashes (high magnification).

Eyelash loss was noted in 23 patients, including 15 who had a Demodex-positive sample ( $p=0.06$ ) (Figure 7). At the interrogation of our patients, 15 were diabetic, 9 had a history of pterygium, 8 had a history of chalazions.

Six cases presented with rosacea, of which 4 cases had Demodex blepharitis (+++) and one case had Demodex blepharitis (++) (Figure 8).

Among our 100 patients, 48 had a Demodex-positive sample, of which 23 (47.9%) were quantified (++) and 25 (52.1%) (+++). They had an average age of 59.71 years. They were 35 women (52.24%, 35/67) and 13 men (39.39%, 13/33). The identification of Demodex was made on direct examination, Demodex folliculorum alone was isolated in 89.6%, Demodex Brevis alone in 4.2%, the two associated species in 6.3%.

Therapeutically, yellow mercury oxide ointment has been used. We treated and controlled the 48 cases of Demodex blepharitis. Among them, 39 (81.3%) had a good evolution marked by the regression of functional and physical clinical signs with negativation of the parasitological examination. Tolerance was good except for 3 patients due to an allergy and the treatment had to be stopped.

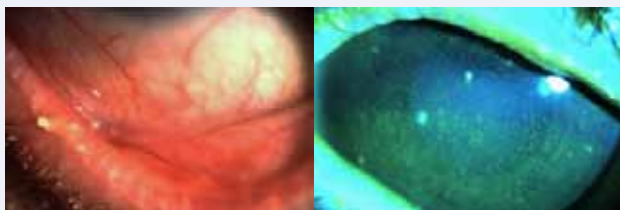


Figure 6 DGM with diffuse kps in Demodex blepharitis.



Figure 7 Patient with Demodex blepharitis complicated by falling eyelashes on the lower eyelids.



Figure 8 Demodex blepharitis associated with rosacea.

Below are the aspects before and after treatment (Figure 9).

### A group of witnesses

It consisted of 48 women and 39 men. The average age was 46 years ( $\pm 18$ ) with extremes ranging from 12 to 85 years.

The presence of Demodex was noted in 12 subjects (13.8%) of which 11 were quantified (++) and one sample (8.3%) (+++). Demodex folliculorum alone was isolated in 83.3%, Demodex Brevis alone in 8.3% and the two associated species in 8.3% of cases.

### Comparison between the two groups

The frequency of Demodex was significantly higher in the



Figure 9 Treatment of Chronic blepharitis with Yellow mercury oxide ointment. a: before treatment, b: after treatment.

sick group (48%) than in the control group (13.8%) ( $p=0.000$ ). Similarly, the quantitative analysis (average number of Demodex per sample) showed a significant difference between the two groups with 52.1% Demodex (+++) for the patients versus 8.3% for the controls ( $p= 0.000$ ).

The identification of Demodex showed that Demodex folliculorum was the most isolated species for the patient group and the control group with 89.6% and 83.3% respectively, with no significant difference between the two groups.

## DISCUSSION

In recent years, many articles have reported the growing interest in the role of Demodex in chronic blepharitis. In our study, the prevalence of Demodex increased with age, affecting mainly the elderly. Indeed, this same finding was made in other studies, this could be explained by the decrease in immunity, the intensification of inflammatory processes and poor eyelid hygiene conditions. The rarity of Demodex blepharitis cases in children and adolescents could be explained by the rarity of sebum and meibum.

Clinically, the scales of Demodex blepharitis often appeared as a whitish, cylindrical sleeve around and at the base of the eyelashes. According to the study by Kabata et al., cylindrical scales around the eyelashes were more present in the group of blepharitis with Demodex than that of blepharitis without Demodex ( $p<0.01$ ) [1].

As in the literature data, we found that the prevalence of MGD increased with the proliferation of Demodex, suggesting the potential role that this parasite could play in the etiopathogenesis of MGD. According to some authors, Demodex would be involved in blocking the follicles and the orifices of the sebaceous glands. But isn't this Demodex and DGM association just a simple coincidence since both have an increasing prevalence with age.

Demodex and especially brevis by parasitizing the meibomian glands could directly interfere with their proper functioning, on the other hand the DGM, by hyperexcretion of lipids, the preferred substrate of Demodex, could promote their proliferation.

Of the 23 patients with eyelash loss, 15 had Demodex. We did not find any significant difference between the fall of the eyelashes and the result of the direct examination ( $p=0.06$ ). Nevertheless, madarosis was slightly more associated with patients with Demodex in the eyelashes.

Some authors have found a correlation between eyelash loss and the presence of Demodex [2-4]. Similarly, the increase in the number of Demodex, occupying deeper regions of the hair follicle, makes the eyelashes fragile, thus promoting their fall [3].

In our study, 6 patients had rosacea. The presence of rosacea has been associated with the presence of Demodex in large numbers in the eyelashes. A meta-analysis showed a significant association between rosacea and the presence of Demodex. The arguments in favor of this association were the importance of the

carriage rate and the density of Demodex in subjects with rosacea compared to controls [4]. It is unclear whether rosacea simply provides an appropriate environment by dilation of the follicular infundibulum, or whether these mites actually play a role in the pathogenesis of rosacea [5-9]. Thus, some authors have suggested that Demodex induces the formation of a perifollicular lymphohistiocytic infiltrate. This cell-mediated immune response would play an important role in the pathogenicity of rosacea [10,11].

Lacey et al., demonstrated antigenic proteins related to a bacterium (*Bacillus oleronius*), isolated from a Demodex folliculorum, capable of stimulating the inflammatory response in patients with rosacea [12].

Demodex is a mite, the most common human ectoparasite, whose involvement in ophthalmic pathology remains debated. Recent studies have shown a greater prevalence of carriage in patients with blepharitis.

In our study, the frequency of Demodex is higher in the sick group than in the control group. This supports the presence of a causal relationship between chronic blepharitis and the presence of Demodex. Our results are similar to data from some studies [13-15]. Some studies, however, did not find a significant difference such as that made by Kemal et al [16], or that of Kabataş et al ( $p=0.18$ ) [1].

The responsibility of Demodex can only be retained by comparing parasitological and therapeutic clinical data.

Zhao et al., reviewed in a meta-analysis they published in 2012, 13 studies and published works on the association of Demodex with blepharitis [17]. In total, these studies concerned 4741 participants (2098 blepharitis and 2643 healthy controls) and the association of the presence of the parasite in blepharitis proved to be statistically significant.

A study of eyelashes in search of Demodex made on 128 people, randomly selected among individuals who consulted an ophthalmological center in Colombia, found this parasite in 63% of patients with blepharitis against 29% of healthy subjects included. The average parasite load was also higher in the case of blepharitis (13 vs 5). Both of these findings were found to be significant [18].

In the study by Demmler et al., Demodex was found in 52% (62/139) of patients with chronic blepharitis versus 29% of controls [19].

A study similar to ours involving 100 sick cases and 100 control cases found a significant difference between the two groups with the presence of Demodex Folliculorum in 63% of the blepharitis group against 33% in the control group ( $p <0.001$ ) [20].

In an Indian comparative study performed on the eyelashes of 72 blepharitis patients and 72 healthy subjects, Demodex was seen in 43% of blepharitis patients and 11.1% of controls. The incidence was higher in people with signs of severe blepharitis.

They concluded that this higher incidence of Demodex in patients with blepharitis suggests that it plays a key role in the clinical manifestations of blepharitis [21].

Demodex brevis and folliculorum are part of the commensal flora. The first is more prevalent in the sebaceous glands and feeds on sebum, while the second prefers to reside in the pilosebaceous unit of the eyelid and feeds on the epithelial cells that line it. They can also feed on other species that inhabit the same space such as Propionibacterium acnes [16,22-24]. Several pathophysiological mechanisms have been put forward to explain the role of Demodex in the genesis of blepharitis.

Indeed, Demodex can be a carrier of bacteria (such as Staphylococcus aureus or Bacillus oleronius) and agents of allergic phenomena in the eyelid, and can therefore aggravate eyelid symptoms and maintain inflammatory phenomena [12].

Similarly, Demodex could disrupt the physiological functioning of the sebaceous glands by the parasite's obstructive action at the level of the Meibomian and Zeiss glands, thus reducing the humidification of the cornea, and by the abrasive action of its claws leading to hyperkeratinization reactions, and epithelial hyperplasia [25]. Also, there would be an inflammatory reaction directed against the parasitic chitin considered as a foreign body. In addition, certain products of parasitic catabolism would stimulate the humoral and cellular immunity of the host [26].

Our results suggest that this parasite is present in carriers of blepharitis as in healthy subjects, however it is more frequently found in patients with blepharitis and with greater colonization. This same observation was made by Glavis-Ramirez et al, who suggest the need to study the presence of Demodex in all patients with blepharitis, especially in cases where cylindrical desquamation was observed in their eyelashes [18].

In our study, as in the literature [17,27-29], D. folliculorum is more frequently isolated than D. brevis. This may be due to a different localization of the two types at the palpebral level. It is known that D. folliculorum is found in the infundibular portion of the hair follicle, while D. brevis is found in the sebaceous gland and its ducts, as well as in the meibomian glands.

The treatment of Demodex sp blepharitis uses several molecules: salicylic acids [30], selenium sulphide [31], metronidazole [32-34], crotonamine [35]. Systemically, a single dose of oral ivermectin, 100 to 200 µg/kg also has a remarkable action on Demodex. Considering the parasite cycle, Holzchuh et al recommend repeating the treatment after seven days. They noted a notable decrease in the number of mites after treatment and an improvement in blepharitis with good tolerance [36]. In our study, 1% yellow mercury oxide was used. Our patients have been improved or completely cured under treatment. The regression of clinical manifestations under specific treatment remains the best argument for the involvement of Demodex in the symptomatology of blepharitis. Several authors agree

that the specific first-line treatment is local by applying an ophthalmic ointment with yellow mercury oxide [19,37-39]. The yellow mercury oxide ointment must be well applied to the base of the eyelashes, once a day preferably in the evening, avoiding any contact with the cornea, a demonstration to the patient beforehand is desirable in this case. An oral H1 antihistamine can be used for intense eyelid pruritus [40].

Rivera et al., recommend application of 2% yellow mercury oxide for 7 days, repeated at 15 days to eradicate the parasite [41].

The duration of treatment varies from 15 to 30 days depending on the Demodex population at sampling and the intensity of the ocular symptoms. This same treatment could be repeated in the event of a recurrence. If this fails, another product can be used.

In several publications, tea tree oil (teatreeoil) in local application would be effective in the eradication of Demodex. This essential oil derived from Melaleuca alternifolia has clearly demonstrated demodectic properties (158,159). In a study conducted in China, treatment with TTO was found to be associated with the prevention of recurrence of Demodex-associated chalazions [42]. However, the clinical efficacy of TTO remains variable and the product seems relatively irritating [43]. A Chinese team worked to identify the active ingredient in TTO, Terpinen-4-ol, which was shown to be effective in vivo in eradicating Demodex. The above finding suggests that the deployment of Terpinen-4-ol alone would be more potent in killing these parasites by reducing the antagonistic effects of other ingredients in the TTO. The latter could be adopted in future formulations to treat Demodex blepharitis [44].

## CONCLUSION

Blepharitis is a frequent reason for consultation in ophthalmology. It can cause aesthetic damage, ocular discomfort, or even corneal damage that affects the visual prognosis. The etiological diagnosis is based on a sample of the eyelashes with a direct examination under the microscope.

Although it is admitted to be a saprophyte of the skin, a large number of arguments plead for the incrimination of Demodex in the etiopathogenesis of chronic blepharitis, hence the interest of a sample of eyelashes with parasitic research in front of any chronic blepharitis or blepharitis resistant to the usual treatments, particularly squamous blepharitis with a cylindrical sleeve around the eyelashes. In case of positive research, a specific treatment will have to be instituted, the effectiveness of which is an additional argument for the etiological diagnosis.

Well diagnosed and well treated, blepharitis, in particular those of parasitic origin, are quite easily controllable with the therapies available to us.

We therefore insist on better management of chronic Demodex blepharitis in order to relieve the patient and ensure his well-being.

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