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ORIGINAL REPORT

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Follicular conjunctivitis in dogs: A retrospective study (2007–2022)

Irene Cerrada[1] | **Marta Leiva**[1,2] | **Rita Vilao**[1] | **Teresa Peña**[1,2] | **Jose Ríos**[3]

[1]Servei d'Oftalmologia, Fundació Hospital Clínic Veterinari, Universitat Autònoma de Barcelona, Bellaterra, Spain

[2]Departament de Medicina i Cirurgia Animals, Facultat de Veterinària, Universitat Autònoma de Barcelona, Bellaterra, Spain

[3]Laboratory of Biostatistics & Epidemiology, Facultat de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain

Correspondence
Marta Leiva, Servei d'Oftalmologia, Fundació Hospital Clínic Veterinari, Universitat Autònoma de Barcelona, Bellaterra, Spain.
Email: marta.leiva@uab.cat

Abstract

Objective: To evaluate the incidence, clinical features, treatment, and outcome of canine follicular conjunctivitis (CFC).

Procedure: Medical records of dogs diagnosed with CFC were reviewed. Data recorded included signalment, duration of clinical signs and treatment details prior to presentation, concurrent ocular/systemic diseases, ocular clinical signs, cytology, treatment, follow-up, and outcome. Blepharospasm, signs of self-trauma, hyperemia, chemosis, ocular discharge, and follicle location and severity (0.5–4) were retrospectively evaluated. Based on severity, treatment consisted of topical 0.1% diclofenac or 0.1% dexamethasone sodium eyedrops. Dogs were classified into young (YD < 18 months) and adult (AD ≥ 18 months).

Results: One hundred and fifty-three dogs (276 eyes) were included in the study: 83YD (54%) and 70AD (46%). Males and bilateral disease were over-represented in both groups. Severity was associated with young age ($p = .032$) and bilaterality ($p = .025$), and not with dermatological diseases ($p > .05$). No differences in follicular location were observed except for more frequent involvement of the nictitating membrane (MN) in YD ($p = .02$). Response to treatment was faster in AD ($p = .001$), with complete resolution in 80.6% of the eyes (100/124) at 1 month. YD treated with diclofenac showed faster resolution than those treated with 0.1% dexamethasone ($p = .009$).

Conclusions: Although CFC is a bilateral ocular disease occurring at any age, the clinical presentation is influenced by age. Follicular conjunctivitis in adult dogs is less sever, less commonly affects the NM, and responds more quickly to topical treatment. One month of topical diclofenac may be adequate for mild cases, and 1 month of topical 0.1% dexamethasone is recommended as initial therapy for moderate to severely affected cases.

KEYWORDS

allergic conjunctivitis, atopy, follicles, papillae, self-limiting conjunctivitis, vernal conjunctivitis

1 | INTRODUCTION

The canine ocular surface is constantly exposed to a wide array of microorganisms. The ability of the ocular surface to recognize and eliminate pathogens is critical to preserve ocular surface health. Therefore, a combination of mechanical, anatomical, and immunological defense mechanisms has evolved to protect the eye.[1,2] Factors such as skull type, eyelid anatomy, the activity and environment of the dog, or the geographical location, all have a major influence on the conjunctiva. Thus, the conjunctiva plays an important role in the response to potentially harmful substances, including microbes and environmental toxins.[1,2] In the dog, the most common conjunctival responses to insult comprise signs of ocular irritation such as blepharospasm, rubbing or self-trauma, various types of ocular discharge, variable hyperemia, chemosis, and the presence of follicles.

In healthy eyes, follicles are only evident on the bulbar surface of the nictitating membrane (NM), where a collection can be observed. However, lymphocytes in the superficial layers of the substantia propria can form follicles in response to antigen stimulation—these are observed throughout the conjunctivae, particularly within the fornices.[1] In those cases, follicles of the bulbar surface of the NM may also increase in number and/or in size.

These lymphoid follicles are the major component of the conjunctiva-associated lymphoid tissue (CALT), whose role is receiving and presenting the antigen to the circulating mononuclear cells.[3] Follicles are easily recognized by the appearance of translucent nodular structures outlined by conjunctival capillaries on the conjunctival surface,[4,5] making the clinical diagnosis of follicular conjunctivitis (FC) straightforward.

In human medicine, conjunctival follicle formation has been described in allergic conjunctivitis, infectious diseases, drug hypersensitivity, sarcoidosis, and as a clinical manifestation of follicular lymphoma.[6–19] Adenovirus has been reported as the most common infectious causative agent,[8,14] followed by *Chlamydia trachomatis*,[7,14,18,20] herpes simplex,[6,14,19] and *Molluscum contagiosum*.[9] Topical anti-glaucomatous drugs, antibiotics, anesthetics, atropine or phenylephrine, among others, have also been related to human follicular conjunctivitis.[10,11,15]

In dogs, follicles in the palpebral or bulbar conjunctiva have previously been associated with chronic antigenic stimulation and allergic conjunctivitis in animals younger than 18 months of age, with a tendency to resolve spontaneously.[1,4,21] Bacterial or fungal etiology in canine follicular development has been excluded by published studies.[22,23] In addition, more chronic conjunctivitis can lead to papillary hypertrophy, where the epithelium proliferates and the conjunctiva folds, imparting a velvet-like appearance.[1] Although CFC is very common, there are few published reports.[7–9]

The purpose of this retrospective study was to evaluate the incidence, clinical features, treatment, and outcome of FC in dogs.

2 | MATERIALS AND METHODS

2.1 | Institutional ethical approval

The internal ethics committee of the *Veterinary Teaching Hospital* of the *Universitat Autònoma de Barcelona* (FHCV-UAB) approved the retrospective use of the data contained in the medical records for the preparation of the present study.

2.2 | Animals and data collection

Medical records of dogs diagnosed with FC by the Ophthalmology Service of the FHCV-UAB, between 2007 and 2022 were retrospectively reviewed. Data recorded included signalment, duration of clinical signs and treatment details prior to presentation, concurrent ocular/systemic diseases, ocular clinical signs, cytology (when available), topical/systemic treatments, follow-up, and outcome.

Inclusion criteria included dogs that were diagnosed with FC after a full bilateral ophthalmic examination by a board-certified ophthalmologist or a resident-in-training, with follow-up data available. To avoid misdiagnosis, animals with follicles restricted to the bulbar conjunctiva of the NM were excluded from the study.

In all the dogs, distant examination, Schirmer's tear test I (MSD Animal Health), basic neuro-ophthalmic evaluation, slit-lamp biomicroscopy (Kowa SL-17®; Kowa Company), rebound tonometry (Tonovet Plus®; Icare Findland Oy), binocular indirect ophthalmoscopy (Heine Omega 500®, Heine) and fluorescein staining (FluoroTouch®, Madhu Instruments) were performed. The bulbar surface of the NM was examined under local anesthesia (Colircusí anestésico®, Alcon cusí, Masnou, Spain).

Special attention was given to signs of ocular irritation such as blepharospasm (Yes/No), rubbing or self-trauma (Yes/No), ocular discharge (Yes/No), degree and specific location of hyperemia (mild, moderate, and severe/bulbar vs. palpebral), chemosis (Yes/No), and the severity and location of follicles. The severity was graded for each eye from very mild (grade 0.5) to very severe (grade 4) based on the number of follicles reported (Figure 1). The location

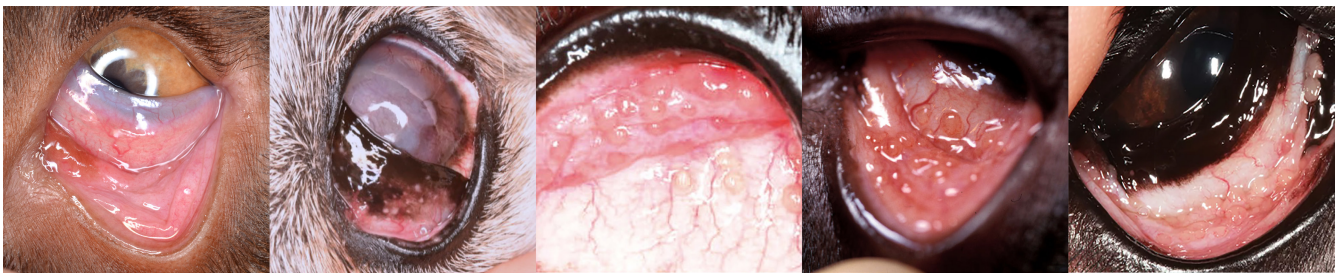

FIGURE 1 Grading of severity according to the number of follicles, from left to right: very mild (grade 0.5), mild (grade 1), moderate (grade 2), severe (grade 3) to very severe (grade 4).

was assigned to palpebral conjunctiva, bulbar conjunctiva and palpebral or bulbar aspects of the NM.

Concomitant systemic diseases were classified as dermatological and non-dermatological. Both groups of diseases were diagnosed after a complete examination by a board-certified dermatologist or internist according to the diagnostic protocols established for each disease.

The selected dogs were divided into two age groups, young dogs (YD < 18 months) and adult dogs (AD ≥ 18 months).

2.3 | Statistical analysis

Quantitative variables were described as median, and their 95% confidence intervals (95% CI) and between-group analysis was performed using the Mann–Whitney *U* test. In the case of qualitative variables, the comparison between groups was performed with Fisher's Exact test and they were described by the absolute frequency and percentage over the study group. Grade of severity was described as qualitative variable and analyzed according to ordinal variable with a Mann–Whitney *U* test. A two-sided Type I error of 5% was established for statistical significance. SPSS Version 26 (IBM Corp. Armonk, NY. USA) was used for all statistical analyses. Dogs with incomplete information for one parameter were excluded for that specific variable.

3 | RESULTS

A total of 153 dogs (276 eyes) met the inclusion criteria. There were 72 entire males, 49 entire females, 11 neutered males and 21 spayed females. The median age was 3 years, ranging from 10 months to 9 years. Several pure and mixed breeds were included, with mixed breeds being over-represented (29 animals, 18.95%), followed by 13 Golden Retrievers (8.5%), eight Labrador Retrievers (5.2%), six English Bulldogs (3.9%), eight English Setters (3.9%), five Border Collies (3.2%), five Weimaraners (3.2%), and 81 dogs of various pure breeds.

Dogs were classified into YD (83 individuals; 54%) and AD (70 individuals; 46%). In both groups, males (48; 57.8%YD vs. 38; 54.3%AD) and bilateral presentation (69; 83.1%YD vs. 54; 77.1%AD) were over-represented. There was no statistically significant over-representation of brachycephalic breeds in either group ($p = .557$).

Previous ocular history was less commonly reported in YD (17 eyes; 11.18% eyes) compared to AD (28 eyes; 22.58% eyes) ($p = .014$). Comorbidities were detected in 47 animals (84 eyes), of which 17 were classified as non-dermatological and 30 as dermatological. Of the 84 affected eyes, 39/152 (25.65%) were YD and 45/124 (36.30%) were AD. Non-dermatological conditions consisted of food allergy (4 dogs, 5 eyes/276; 1.80%), gastritis (1 dog, 2 eyes/276; 0.72%), gastroenteritis (3 dogs, 6 eyes/276; 2.17%), epilepsy (1 dog, 2 eyes/276; 0.72%), chronic kidney disease (1 dog, 2 eyes/276; 0.72%), leishmaniasis (4 dogs, 8 eyes/276; 2.90%), traumatic pneumothorax (1 dog, 1 eye/276; 0.36%), immune-mediated sacculitis (1 dog, 1 eye/276; 0.36%), and intrahepatic shunt (1 dog, 2 eyes/276; 0.72%). Atopy was the most common dermatological condition in both groups and especially in AD (18 dogs, 33/124 eyes; 26.61% AD vs. 10 dogs, 18/152 eyes; 11.84% YD) ($p = .033$). Other dermatological conditions included demodicosis (1 dog, 2 eyes/276; 0.72%) and zinc-responsive dermatosis (1 dog, 2 eyes/276; 0.72%).

Topical treatment prior to presentation included broad-spectrum antibiotics in 59/276 eyes (21.37%), dexamethasone in 26/276 (9.42%), NSAIDs in 14/276 (5.07%), and 0.2% cyclosporine in 9/276 (3.26%). In addition, five dogs were under systemic treatment for concurrent systemic diseases: amoxicillin-clavulanic acid and prednisolone, allopurinol, lokivetmab, oclacitinib maleate, and trimethoprim-sulfamethoxazole, one dog each.

The most common presenting complaints were redness, blepharospasm and ocular discharge, varying in duration from 4 days to 6 months. FC was an incidental finding in some patients with concurrent ocular disease—in those patients, the present complaint varied from anisocoria to oral pain. Table 1 summarizes the ocular clinical signs, location and severity of the follicles recorded. All

TABLE 1 Clinical signs in dogs affected with follicular conjunctivitis.

Clinical signs	All, 276 eyes (153 dogs)	YD, 152 eyes (83 dogs)	AD, 124 eyes (70 dogs)	*p*-Value
Blepharospasm (%)	32 (11.59)	17 (11.18)	15 (12.09)	0.146
Rubbing or self-trauma (%)	2 (0.7)	2 (0)	0 (0)	ND
Hyperemia (%)				
Location				
Palpebral	171 (61.95)	80 (52.63)	91 (73.38)	0.542
Bulbar	49 (17.75)	32 (21.05)	17 (13.70)	0.253
Severity				
Mild	119 (43.11)	46 (30.26)	73 (58.87)	0.182
Moderate	118 (42.75)	77 (50.65)	41 (33.06)	0.244
Severe	39 (14.13)	29 (19.07)	10 (8.06)	0.435
Chemosis (%)	3 (1.96)	2 (1.31)	1 (0.80)	ND
Ocular discharge (%)	239 (86.59)	138 (90.79)	99 (79.83)	0.651
Follicle (%)				
Location				
Palpebral	124 (89.86)	68 (44.7)	56 (45.16)	0.798
Bulbar	43 (30.80)	26 (17.10)	17 (13.70)	0.613
Palpebral surface NM	99 (72.39)	50 (32.89)	49 (39.50)	0.191
Bulbar surface NM	89 (62.55)	62/134 (46.27)*	27/104 (25.96)*	**0.002**
Severity (number of follicles)				
Grade 0.5	26 (19.62)	9 (5.92)	17 (13.70)	**0.032**
Grade 1	62 (40.52)	29 (19.07)	33 (26.61)	**0.032**
Grade 2	63 (41.17)	38 (25)	25 (20.16)	**0.032**
Grade 3	33 (21.56)	21 (13.81)	12 (9.67)	**0.032**
Grade 4	8 (5.22)	3 (1.97)	5 (4.03)	**0.032**

Note: Data are shown in eyes and percentages. Numbers in bold letters are statistically significant. (YD: dogs <18 months; AD: dogs 18 months; ND: no data; *: incomplete data).

parameters were recorded for all animals, except for the location of the follicles on the bulbar surface of the NM, which was assessed only in 238/276 eyes.

The severity of follicles was statistically greater in YD (more 2 and 3 grades) than in AD (more 0.5 and 1 grades) ($p = .032$) and was not associated with atopy in either group ($p = .892$). Considering all dogs, YD and AD, unilateral cases showed less severity (more 0.5 and 1 grades) than bilateral cases (more 2, 3, and 4 grades) ($p = .025$). The distribution of the follicles was very similar in both groups except for the more frequent involvement of the bulbar surface of the NM in YD (62 eyes; 46.27% vs. 27 eyes; 25.96% AD). In addition, statistical differences between the two groups were observed only for this particular location ($p = .020$).

Concurrent ocular diseases included chronic dry eye (10/276 eyes; 3.62%), anterior uveitis (5/276 eyes; 1.81%), corneal ulcers (3/276 eyes; 1.08%), optic neuritis atrophy, periocular abscess, and phthisis bulbi (1/276 eyes; 0.36%, each).

Conjunctival cytology was performed in only five eyes (5/276; 1.8%). All eyes were severely affected and showed a predominantly lymphoplasmacytic cellular infiltrate.

All dogs received topical anti-inflammatory medication for the treatment of the FC, either 0.1% diclofenac sodium solution (Voltaren®, Théa Laboratories, Barcelona, Spain) or 0.1% dexamethasone solution (Maxidex®, Alcon Laboratories, Barcelona, Spain). Based on the more limited effects of NSAIDs on the synthesis and action of inflammatory mediators compared to corticosteroids, diclofenac was used in all the cases graded as mild (grades 0.5 or 1) or when a concomitant ocular condition precluded the use of corticosteroids [corneal ulcers (three eyes)]. For YD, 38 eyes were treated with diclofenac (25%) versus 114 eyes treated with steroids, and for AD, 53 eyes were treated with diclofenac (42.74%) versus 71 eyes treated with steroids ($p = .255$). The posology differed according to the severity and ranged from 1 drop twice a day to 1 drop four

times a day in the affected eye until the first follow-up visit, which was scheduled at 1 month at our institution. If signs of FC persisted, medication was continued until the next review at 2 months (1 month after the first follow-up). If the signs of FC had resolved, treatment was either discontinued (diclofenac) or tapered and discontinued over 2 weeks (dexamethasone).

At the first follow-up (1 month), resolution of clinical signs was observed in 100 eyes of AD (80.64%) and in 94 eyes of YD (61.84%) ($p = .001$). In both groups, the healing time was shorter in eyes treated with diclofenac [median 26 days (95% CI 7; 30) in YD and median 21 days (95% CI 14; 45) in AD] than in those treated with dexamethasone [median 30 days (95% CI 30; 50) in YD and median 30 days (95% CI 30; 45) in AD], nevertheless, this difference was statistically significant only in YD ($p = .009$).

4 | DISCUSSION

This is the first retrospective characterization of CFC, evaluating the clinical features, comorbidities, and response to treatment. Published data on this disease are scarce and textbook based, therefore the discussion is mainly based on human literature. Among all types of human conjunctivitis, vernal allergic conjunctivitis (VC) and trachoma show the greatest similarity to CFC.[10,20,24]

Young human patients are more commonly affected by VC or trachoma and young dogs by FC.[1,4,5,25] Indeed, in the present study, follicles were more common in dogs younger than 18 months, mirroring the young age of patients with VC (5–25 years, with an onset at 6–7 years of age).[10] Additionally, VC tends to resolve spontaneously after puberty, when the presumed overexpression of conjunctival sex hormones (estrogen and progesterone) begins to decrease.[10,25,26] This may explain why young dogs in our study were more frequently and more severely affected than adults.

Contrary to what has been described for VC, where boys are more likely to be affected than girls, this study found no gender predisposition for CFC. However, gender susceptibility becomes equal after puberty in both conditions.[10]

Anatomical factors such as skull type and eyelid anatomy, may play a role in the conjunctival response to potentially harmful substances.[1,2] In the herein, brachycephalic breeds showed no predisposition to CFC, which could be explained by the physiologic exophthalmia which, by moving the eyelids forward, reduces the conjunctival sac, thus diminishing the possibility of harvesting foreign bodies or contact with allergens.

The differences between CFC, VC and trachoma are mainly reflected in the clinical presentation, pathogenesis, and histology. Bilaterality is a common feature of the three diseases,[10,27] but the clinical hallmark differs between them. CFC is manifested by follicles[4] (translucent nodular structures outlined by capillaries), VC by giant papillae (inflammatory thickening with central blood vessels), and trachoma by both features. In addition, VC and trachoma may induce formation of pseudomembranes and scarring, features that have not been previously reported in CFC literature, nor observed in our study.[10,18,28] Although the mechanisms of scar formation are not fully understood, chronicity, severity, etiologic agent, differences in the inflammatory infiltrate and necrosis grading, may play a role in its development. In trachoma, conjunctival scarring has been found to result from follicular necrosis, inducing "star-shaped" scars and semilunar limbal scars, or Herbert's pits.[7] The latter is formed by the thinning of the superior cornea as the follicles heal.[18] In VC, scarring is shown as punctate limbal epithelial keratopathy, or Trantas' dots.[10] Those consist of clumps of necrotic eosinophils, neutrophils, and epithelial cells collected in crypts at the junction of the cornea and conjunctiva.[29]

The distribution of follicles varies among diseases, being more prevalent on the limbal and/or dorsal bulbar conjunctiva in VC[10]; and on the palpebral conjunctiva and fornices in trachoma. In the present study, the NM was more frequently involved than the other regions, followed by the palpebral conjunctiva. Interestingly, a recent study in dogs localized pronounced allergic reactions more frequently in the ventral conjunctiva and NM, where most allergens accumulate.[30] This finding would suggest an allergic origin for CFC in our study.

Although the pathogenesis of allergic conjunctivitis historically described follicle formation,[1,31,32] in a recent study follicles are not a common feature.[30] This could question whether "allergy" is a truly trigger for follicle formation. Despite the aforementioned publication, we understand that atopy should be considered as one of the potential etiologies for follicle formation. Further studies are needed to establish the etiopathogenesis of this common condition. In this study, atopy was the most common systemic comorbidity, with a higher incidence in AD, possibly explained by the usual late onset of canine atopy (between 6 months and 3 years of age).[33] Similarly, allergic conjunctivitis has been associated with atopy, in both humans and dogs, with incidences of 25%–45%[34,35] and 94%,[30] respectively. Similarly, VC, considered an allergic disease, has classically been associated with atopic diseases such as asthma, allergic rhinitis, or atopic dermatitis.[36–38] Notwithstanding, recent studies suggest a different pathogenesis from the classically considered Type 1 IgE-mediated hypersensitivity,[39] with skin tests often negative in people affected with VC. Trachoma, which has a bacterial etiopathogenesis

(*Chlamydia trachomatis*), has not been associated with atopy.

Histopathology facilitates the diagnosis of these three diseases. Although CFC has not been histologically characterized, VC and trachoma have been extensively described. The conjunctival giant papillae, commonly seen in VC, are formed by deposition of mixed cellular infiltration and new collagen, whereas the follicles seen in trachoma are composed mainly of lymphoid tissue.[4,10,18,32,40,41]

Diagnosis of these three diseases is mainly based on clinical criteria and conjunctival cytology. Mast cells, basophils and eosinophils are predominant in VC,[10] whereas intracytoplasmic inclusions of *C. trachomatis* are the hallmark of trachoma. Contrarily to these human diseases, the cellular response in CFC is predominantly lymphoplasmacytic with a low eosinophilic component,[1,4] which was consistent with the cytology results in this study. In addition, biopsy, although more invasive, has been proven to be a valuable diagnostic tool. Other less commonly used diagnostic methods encompass cell culture, immunofluorescence, enzyme immunoassay, serology, PCR, allergy testing, tear cytology, and evaluation of tear IgA levels and proinflammatory cytokines.[10]

In human medicine, VC and trachoma may resolve without treatment. If needed, topical treatment will depend on the etiology, severity, and systemic and ocular concomitant diseases. The therapeutic approach is very similar for CFC and VC, consisting of anti-inflammatories, immune-modulators and mast cell stabilizers. In terms of anti-inflammatory agents, topical corticosteroids are considered the gold standard treatment for CFC, whereas in VC they are reserved only for severe or refractory cases. NSAIDs have also been used, although usually for mild cases.[10,42,43] The use of immunosuppressive agents, such as topical cyclosporine, montelukast, tacrolimus, sirolimus, and mitomycin-C has been described for refractory cases in humans.[10,42,43] Mast cell stabilizers and antihistamines are frequently prescribed for VC, being of questionable efficacy for CFC.[1,4] Occlusive treatments (patching, occlusive goggles or tarsorrhaphy) and contact lenses (to avoid friction from the enlarged palpebral papillae) are also used in human ophthalmology to provide relief.[10,42,43] Avoidance of the allergen with saline conjunctival irrigation or artificial tears has been described in VC[10,42,43] and CFC[32] to reduce follicle formation and is of particular interest in dogs with deep fornices where large amounts of irritants or allergens can be housed.

In humans, systemic treatment is infrequently used because of its side effects. The veterinary literature only recommends systemic therapy when there is concurrent skin disease.[1,4,32]

In veterinary medicine, follicular debridement has been supported by some authors for refractory cases, although it may exacerbate the situation by predisposing to chronic conjunctivitis.[24] Certainly, there are no published data on its benefit. In human medicine, cryotherapy and CO_2 laser have been described for refractory VC cases, although their long-term efficacy is unclear.[10,42,43] In the authors' opinion, the integrity of the mucosa-associated lymphoid tissue should be maintained, therefore debridement was avoided in this study.

In the herein, clinical resolution at 1 month follow-up was 74.05%, being higher in AD (80.64% eyes) than in YD (61.84% eyes). The results showed a faster resolution in YD treated with diclofenac sodium compared to dexamethasone. It should be noted that most of the animals treated with the NSAIDs were mildly affected, thus the results may be related to a low severity of the condition rather than to a major anti-inflammatory effect of the NSAIDs.

This study has several limitations owing to its retrospective design. Limitations include the variation of treatment, the short follow-up period, the lack of data for some specific parameters (follicular location), and the potential bias in the severity criteria—the assessment of the number of follicles is subjective and needs to be compared with previous apprehended scores. Undoubtedly, a prospective study, with a more sophisticated and standardized grading system, may help to better characterize the disease. It is also worth noting that in a large population, mild cases of CFC may be underdiagnosed, which could influence the results.

In summary, canine follicular conjunctivitis is a predominantly bilateral ocular disease affecting dogs of all ages, although age induces variability in its clinical presentation. While YD are more commonly and severely affected, have bilateral presentation and a more frequent NM involvement, AD show milder severity and a higher incidence of concomitant atopy. One month of topical diclofenac may be adequate for the mildly affected cases, while 1 month of topical 0.1% dexamethasone is recommended as a starting point treatment for the moderately to severely affected cases.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Irene Cerrada https://orcid.org/0000-0002-0665-0202
Marta Leiva https://orcid.org/0000-0003-2378-0946
Rita Vilao https://orcid.org/0000-0002-6513-0397
Teresa Peña https://orcid.org/0000-0001-8809-5566
Jose Ríos https://orcid.org/0000-0002-0716-8784

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