

WHAT IS IT “DRY EYE” AND HOW TO TREAT IT?

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STRESZCZENIE

CO TO JEST SUCHE ZAPALENIE SPOJÓWEK I ROGÓWKI I JAK JE LECZYMY?

Suche zapalenie spojówek i rogówki u zwierząt (KCS) powstaje na skutek zubożonej produkcji łez, co skutkuje ich niedoborem. Choroba objawia się wysuszeniem powierzchni oka. Oko jest zaczerwienione, zwierzę odczuwa świąd. Pojawiają się na powierzchni rogówki keratopatie. Schorzenie występuje u psów, kotów a nawet koni. W miarę trwania choroby, wokół oczu na powierzchni powiek, odkłada się ropna wydzielina. Istnieje wiele przyczyn powodujących taki stan. Głównie są to zaburzenia natury immunologicznej, wady wrodzone, urazy, reakcje polekowe, infekcje wirusowe oraz zaburzenia hormonalne. Rozpoznanie choroby odbywa się za pomocą testu łzowego Schirmera (STT). Leczenie polega na podawaniu preparatów nawilżających oko oraz leków stymulujących produkcję łez (cyclosporyna A, tacrolimus). W przypadku, gdy leczenie takie nie przynosi oczekiwanych rezultatów, można zastosować zabieg transpozycji przewodu ślinianki.

SUMMARY

Keratoconjunctivitis sicca – KCS- “dry eye” is due to an aqueous tear deficiency. This results in persistent, mucopurulent conjunctivitis and corneal ulceration and scarring. KCS occurs in dogs, cats and horses. With time, some of the mucous can build up around the eye, becoming dry and crusty. As the conditions progresses, the cornea becomes invaded with blood vessels, scarred and pigmented. There are a number of possible causes i.e. autoimmune, congenital, trauma, drug reactions, viral infections and hormone imbalance. Dry eye is diagnosed with a Schirmer tear test. Therapy consists of artificial tear solutions, ointment and antibiotic combinations. Lacrimogenics such as topical cyclosporine A or tacrolimus may increase tear productions. In chronic KCS refractory to medical therapy, parotid duct transposition is indicated.

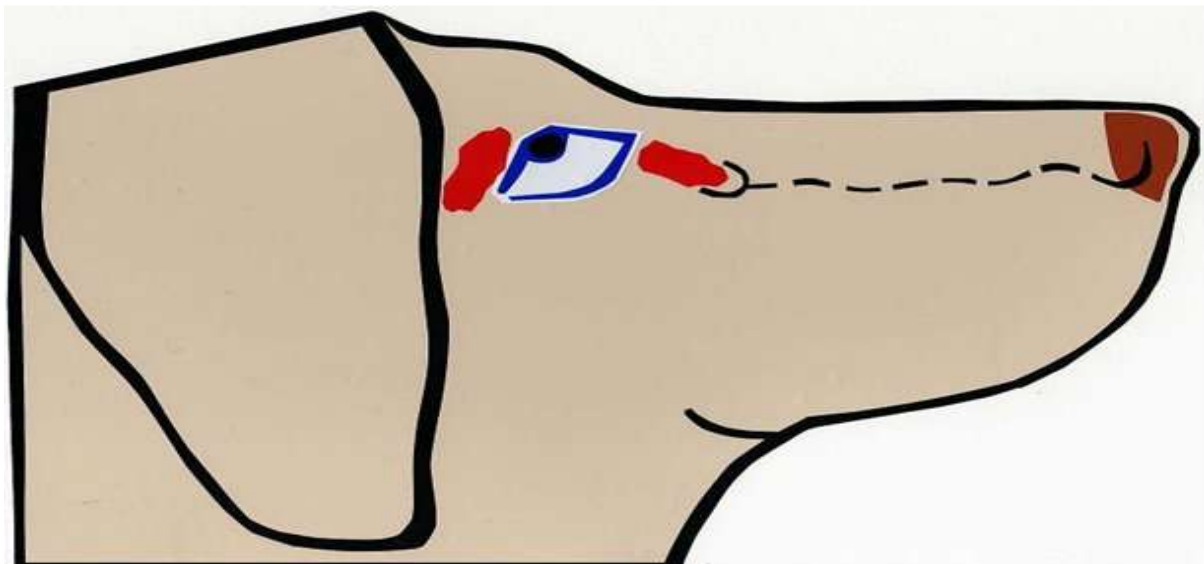
KEY WORDS : KCS, Dry eye, Cyclosporine A, Tacrolimus, Parotid duct transposition

INTRODUCTION

Tears are essential to the comfort of the eyes. Without tears, eyes become irritated. An adequate supply of tears covering the partially exposed anterior segment of the globe and associated adnexa is necessary for optical integrity, maintenance of the cornea and normal eye function. This fluid is called the precocular tear film PTF (Samuelson). Without tears (KCS) develops (Bryla).

Anatomy of the lacrimal system

The lacrimal system consists of a secretory and an excretory component. These components are responsible for production and excretion of the tear film (Hartley, Williams i Adams). The lacrimal system in animals consist of the orbital lacrimal gland and the third eyelid gland, which secretes tears. The orbital lacrimal glands lies over the upper, outer corner of the eye. Its excretory ducts branch downward toward the eyeball. A constant stream of tears washes of the eye and is drained off through two small openings located in the inner corner of the eyelids. Through these openings the tears pass into the lacrimal canaliculus, then through the lacrimal sac into the nasolacrimal duct and finally into the nasal cavity (Riberio, da Cunha Brito i da Costa Martins). Some animals have an accessory opening in the canal as it pass by the root of the upper canine tooth (Samuelson).



Ryc.1. Lacrimal apparatus in dog.

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Histologically, the gland is a mixed tubuloalveolar type. Its function is production of the serous portion of tears (Samuelson). Connective tissue, blood vessels and nerve fibers comprise the glandular stroma. Male lacrimal glands are larger than females once. The orbital lacrimal and third eyelid glands are innervated by sympathetic and parasympathetic nerve fibers and primary control is mainly exerted by the parasympathetic nervous system (Riberio, da Cunha Brito i da Costa Martins). Clinically, certain cholinergic drugs e.g. pilocarpine will stimulate tear secretion, whereas other drugs i.e. anticholinergics will decrease tear secretion (Samuelson). Tears are present over the surface of the eye as a triple-layered film. The outer, thin, superficial oily layer is provided by sebaceous gland of Zeis and the Meibomian glands. This layer reduces evaporation of the underlying aqueous tear and forms a barrier along the lid margins that prevents overflow onto the face (Samuelson). The intermediate or aqueous layers is secreted by the orbital gland (60%) and third eyelid glands (40%) and is the largest layer of the tear film, measuring approximately 7 μm . In addition to water, this layer contains electrolytes, glucose, urea, active surface polymers, glycoproteins and lacrimal proteins, including immunoglobuline A, albumin, beta-lysine, lysozyme and lactoferrin (Riberio, da Cunha Brito i da Costa Martins). The third, innermost layer is the mucin layer, which is produced by the conjunctival goblet cells. This mucin layer absorbed to the corneal epithelial surface and distributed evenly during normal blinking. The mucin provides a hydrophilic surface over which the aqueous tear fluid spreads evenly (Samuelson). The main function of the third layer is to correct corneal surface irregularities, in addition to promoting tear adhesion to the corneal epithelium (Grahn i Storey).

Causes of the dry eye

There are many causes of KCS. Studies support that most cases of dry eye in dogs are the result of immunomediated disorders since affected animals frequently exhibit T- cell infiltration in the lacrimal glands (Riberio, da Cunha Brito i da Costa Martins). The immune system identifies the dog's own tear glands as “foreign”, and attempts to destroy them. As a result, tear production is progressively reduced, and left untreated, can be lost all together. There is circumstantial evidence that the disease resembles Sjögren's syndrome in human. This syndrome is a systemic autoimmune disease characterized by KCS, xerostomia and plasmacytic lymphadenitis as also described in dogs (Riberio, da Cunha Brito i da Costa Martins) (Kański). Other sources of dry eye include drug toxicity. The sulfa drugs (Tribisen) are notorious for causing KCS. The mechanism of action of sulfonamides in KCS is not completely understood, but it is believed to be a response of T cells to haptens generated by oxidative metabolites derived from these substances (Wilkie i Wolf). Some dogs are born with defective tear glands (as described in certain lines of Yorkshire terrier), (Bryla) (Hartley, Williams i Adams). Also procedures performed under general anesthesia lasting longer than two hours can lead to a significant decrease in tear production (Herring). Removal of the third eyelid tear producing gland ,

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instead of replacing the gland in its proper location during surgery for “Cherry eye” can lead to KCS (Izci, Celik i Alkan). Likewise, damage to the facial nerve was found to be associated with iatrogenic KCS (Samuelson) (Riberio, da Cunha Brito i da Costa Martins). Recently, cyclophotocoagulation of the ciliary body with the laser for the treatment of glaucoma in dogs has been recognized as a potential cause of dry eye (Riberio, da Cunha Brito i da Costa Martins). KCS is thought to be by some viral infections like canine distemper . In cat dry eye has been associated with chronic feline herpesvirus-1 infection. In horses, KCS may follow head trauma (Riberio, da Cunha Brito i da Costa Martins). There is also thought to be a connection between metabolic disease like: hypothyroidism, hyperadrenocorticisms and diabetes mellitus and KCS (Williams, Pierce i Mellor). Decreased lipid layer production is observed in older dogs and is due to abnormal secretion of the tarsal gland (Riberio, da Cunha Brito i da Costa Martins).

Clinical signs

The earliest symptoms of KCS is conjunctivitis, or inflammation of the inner eyelids. As the condition develops, mucous threads may be noticed on the surface of the eye, which move as the dog blinks, or build up at the bottom of the eye, near the lower lid. It occurs when there is a deficiency in the water portion of the tear film which normally accounts for 95% of the tear volume (Samuelson). The condition progresses to keratitis, inflammation of the cornea. Dog will often show signs of discomfort, and corneal ulcers are frequently present at this stage (Bryla). Certain signs are highly suggestive of dry eye including: red, irritated or bloodshot eyes, clouding or pigmentation of the cornea and reduced vision (Miller i Smith). Any dogs are affected by dry eye (KCS), but some breeds are predisposed. These include: Westies, Cocker Spaniels, Yorkshire Terriers, Jack Russel Terriers, Lhasa Apso, Labradors. Springer Spaniels, Shit Tzu, Bull Dogs, Collies. The conditions can occur at any age, but is most commonly seen in dogs of 6 to 10 year of age (Bryla) (Riberio, da Cunha Brito i da Costa Martins) (Miller i Smith).

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Phot.1. Keratoconjunctivitis sicca in Yorkshire Terrier.

Diagnosis

Keratoconjunctivitis sicca can be diagnosed by the Schirmer tear test (STT).



Phot. 2. Schirmer tear test - STT.

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Two types of the STT have been described (STT-1 and STT-2). STT-1 measures basal and reflex tear production and is the most commonly used test. The STT-2 evaluates basal tear production after topical application of an anesthetic and of predictive values in animals with corneal ulceration which do not tolerate the STT-1 (Bryla) (Riberio, da Cunha Brito i da Costa Martins). To perform the STT-1 test, a strip of special paper is inserted inside the lower eyelid in the outer corner of the eye for 60 seconds (Hamor, Roberts i Severin). The moisture of the eye will wet the paper. At the end of the 60 second period, the height of the moistened area is measured.



Phot.3. Measuring of STT-1.

A height of 15 mm or more is normal. A height 11 – 14 mm is a borderline results, but the less than 10 mm means the eye is dry. A height less than 5 mm the eye is severely dry (Miller i Smith).

In the STT-2 normal values are 4 – 5 mm/min (Riberio, da Cunha Brito i da Costa Martins) (Hamor, Roberts i Severin). Animals with dry eye condition should also be checked for the presence of corneal ulcers. This is achieved by performing the Fluorescein Stain Test (Bryla). An alternative method for the estimation of tear production in dogs is the phenol-red-thread test. This test lasts only 15 seconds. Reference values for dogs ranges from 30 – 38 mm/15 seconds (Grahn i Storey).

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Qualitative tear film production is measured by the tear film breakup time (BUT). This time is evaluated by biomicroscopy using a cobalt blue filter after topical installation of fluorescein. The normal (BUT) time in dogs is 20 or more seconds. Less than 20 seconds are considered to indicate KCS (Riberio, da Cunha Brito i da Costa Martins).

Treatment of “Dry eye”

The successful therapy for KCS is the use of lacrimomimetics, lacrimostimulant medications and anti-inflammatory agents (Bryla) (Riberio, da Cunha Brito i da Costa Martins). If the cause of the dry eye is known, than treatment should be aimed towards eliminating it (Wilkie i Wolf). Unfortunately, in many cases, the cause of the KCS is never known (Riberio, da Cunha Brito i da Costa Martins). Most cases of dry eye are managed rather than cured. There are two types of long term medical treatment for dry eye; artificial tears, used to wet the eye, and drugs which stimulate tear productions. Treatment may include also topical antibiotics and clean the eye and keep them free of discharge, especially before applying medication (Bryla). Artificial tears are slightly viscous drops or ointments that wet the eye. The problem with these is that they have to be applied to the eye very frequently. Typically this means every two hours or more frequently. There are a number of brands available in different formulations containing hypromellose, dextran, carboxymethylcellulose, chondroitin sulfate, and polyacrylic acid (Bryla) (Riberio, da Cunha Brito i da Costa Martins) (Miller i Smith). A breakthrough came with the discovery of lacrimostimulants like cyclosporine A (Madany i Wiśniewska).



Phot.4. Optimmune produced by Intervet.

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Other lacrimostimulants now known are : pimecrolimus, tacrolimus, diquafosol tetrasodium, cholinergic drugs (pilocarpine) and nerve growth factor NGF (Riberio, da Cunha Brito i da Costa Martins) (Berdoulay, English i Nadelstein) (Kaswan).

Cyclosporine are non-cytotoxic agents. It inhibits T-helper cell activity and shifts the regulations of the immune response towards immune tolerance (Kaswan). Topical cyclosporine has several beneficial effects in dry-eye patients. One of these effects is to increase secretion of physiologic tears. Physiologic tears, as opposed to the artificial tears, contain growth factors to regulate corneal-cell turnover and healing, lysozyme and antibodies for infection control and numerous nutritional elements required for the health of the avascular cornea. Topical CsA appears to facilitate lymphocytic apoptosis and suppress epithelial-cell apoptosis, allowing regeneration of lacrimal gland. Cyclosporine also restores goblet-cell mucin production (Madany i Wiśniewska) (Kaswan). The majority of KCS dogs require lifelong CsA- treatment. Interruptions in therapy lead to relapse of KCS (Kaswan). Cats have a lower tolerance to this ocular irritation than do dogs (Kaswan). Recommended frequency is usually twice daily and can be adjusted more or less frequently to effect. Topical use of 0,2% CsA is safe and does not favor the occurrence of ocular infections (Riberio, da Cunha Brito i da Costa Martins).

Pimecrolimus is an ascomycin derivative which selectively interferes with the activation of T cell and mast cells, inhibiting the production of inflammatory cytokines. In veterinary ophthalmology topical application one drop, 3-times a day of a 1% solution was able to increase STT values in dogs with KCS and to reduce corneal inflammation with superficial keratitis. The superiority of pimecrolimus might be attributed to its low molecular weight compared to CsA (Riberio, da Cunha Brito i da Costa Martins).

Other lacrimostimulant used in KCS treatment is tacrolimus. This is macrolide antibiotics, which is 10 to 100 times more potent in vitro than CsA. A topical aqueous solution of 0,2% tacrolimus was found to be effective in increasing tear productions in dogs with dry-eye (Riberio, da Cunha Brito i da Costa Martins) (Berdoulay, English i Nadelstein).

Diquafosol tetrasodium is a new dinucleotide which functions as an agonist at the P2Y2 receptors and has been developed for the treatment of dry eye in humans. The drug promotes nonglandular secretion of fluid probably by water transport via activation of chloride channels, as well as the secretion of mucin and possibly the production of lipids by meibomian glands. Diquafosol was found to be safe and rapidly metabolized on the ocular surface (Riberio, da Cunha Brito i da Costa Martins).

In the lacrimal gland, cornea and tear film were discovered TrKA receptors. These receptors bind nerve growth factor - NGF. Topical administration of 100 µl of NGF twice daily was shown to

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significantly increase STT values, corneal sensitivity and mucin production (Riberio, da Cunha Brito i da Costa Martins) (Coassin, Lambiase i Costa) (Keratoconjunctivitis sicca.).

Veterinary ophthalmologist have been administering pilocarpine at 1% or 2%, topically or systemically as an adjuvant to the treatment of neurogenic KCS in dogs unresponsive to CsA. Administration of pilocarpine can cause side effects due to parasympathetic intoxication. Dilution of pilocarpine to a concentration of 0,25% in artificial tears minimizes the occurrence of inflammatory reactions (Riberio, da Cunha Brito i da Costa Martins).

While most cases of KCS can be successfully managed with long-term medications, some animals may not respond favorably. Such patients needs surgical procedure. The surgical procedure recommended is the Parotid Duct Transposition. However, the procedure can led to side effects such as the formation of calcium granules retained in the tarsal plate, which may obstruct the transplanted duct (Riberio, da Cunha Brito i da Costa Martins) (Keratoconjunctivitis sicca.).

Dry eye in most animals carriers a good prognosis for successful treatment, but is dependent on the underlying cause. Treatment is generally most successful if it is diagnosed early and medical therapy is consistently administered as prescribed (Eaton Seth).

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