Keratoconjunctivitis sicca ("Dry Eye")

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Introduction and Overview

Keratoconjunctivitis sicca (KCS) is a disease of the eyes, characterized by inflammation of the cornea and conjunctiva. This condition occurs secondary to a deficiency in formation of the tear film that normally protects the cornea (Best et al, 2014), which leads to dry, irritated eyes. As a result, KCS is commonly known as "dry eye" or in veterinary terminology, xerophthalmia. This disease occurs often in West Highland White Terriers, but is also common in many other breeds, including Lhasa Apso, English Bulldog, American Cocker Spaniel, English Springer Spaniel, Pekingese, Pug, Chinese Shar Pei, Yorkshire Terrier, Shih Tzu, Miniature Schnauzer, German Shepherd, Doberman Pinscher, and Boston Terrier. While the reported incidence of KCS across all dog breeds ranges from 1% to 2%, there appears to be an increased predisposition reported for both neutered male and female dogs, and for female West Highland White Terriers, in particular.

Relevant Anatomy of the Eye

To understand how KCS develops and ultimately how it is treated, if is important to have a good appreciation of the relevant anatomy of the eye and the glands that produce tears. The relevant components of the eye are the clear outer cornea, the conjunctiva, the eyelids, and the Meibomian and lacrimal glands **(Figure 8.3)**. The Meibomian glands are located along the edge of the eyelid. There are two lacrimal glands associated with each eye. One lacrimal gland is located slightly above and lateral to the eye, and the other is located medially by the third eyelid (also called the nictitating membrane.

How Tears Are Produced

The tear film that covers the eyes is made up of three distinct layers. The outermost layer is made up of oils, which are secreted by the Meibomian glands. This lipid layer provides protection against evaporation, binds the tear film to the cornea, and prevents tears from simply pouring out over the lower eyelid onto the face. The middle layer of the tear film is the aqueous layer, which is produced by the lacrimal glands. As its name would suggest, the aqueous layer consists primarily of water, along with important proteins and enzymes that help remove bacteria and cellular waste material, and lubricate the surface of the cornea. The innermost layer of the tear film is the mucin layer, which is is produced by tiny secretory cells in the conjunctiva known as goblet cells. The mucin layer facilitates the spread of the tear film over the cornea.

What causes Keratoconjunctivitis sicca?

There are several potential causes of KCS in dogs, which include immune disorders that destroy the lacrimal tissue, diseases that affect the conjunctiva and lacrimal tissue, congenital conditions in which the lacrimal tissue fails to develop, medications, traumatic incidents and treatments. The common feature among these causes is that they impair the ability of the tear-secreting tissues in the eye to perform their basic functions, with the end result being the development of "dry eye".

Common Clinical Findings
West Highland White Terriers at Risk
Red, Irritated Eyes
Pawing at Eyes
Ocular Discharge

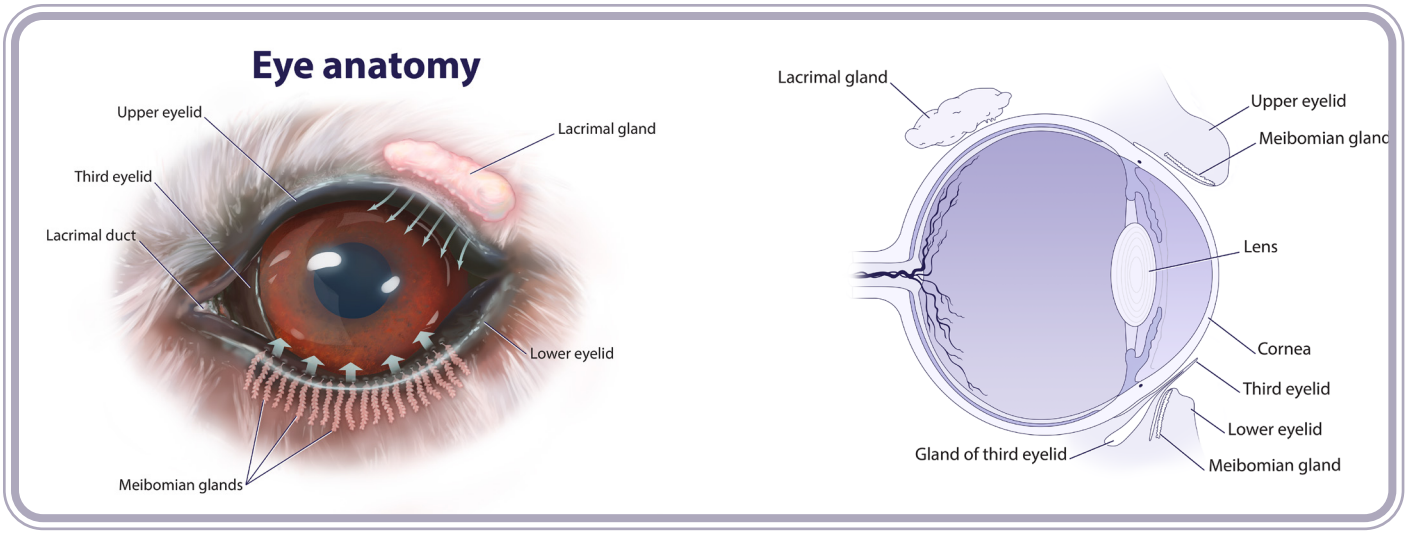

Figure 8.3 - Two illustrations depicting the important anatomical features of the dog, particularly the locations of the lacrimal and Meibomian glands that are critical to the secretion of the tear film.

Immune-Mediated Adenitis: The most common cause of KCS is immune-mediated lacrimal adenitis, which means that the body's own immune system is causing abnormal inflammation of the lacrimal glands. The underlying reason why the immune system targets the lacrimal glands for destruction is unknown, but the end result is infiltration of the glands with lymphocytes and the inability to produce the aqueous layer of the tear film. There does not appear to be a specific breed predisposition to this condition.

Congenital Acinar Hypoplasia (Congenital Alacrima): As its name implies, this condition is genetic in origin and the term 'alacrima' literally means "no tears." This is an autosomal recessive trait in which the responsible allele is carried on the non-sex determining chromosomes. Thus, if two animals having the recessive trait for alacrima mate, there is a 25% chance that the offspring will inherit the disorder. Breeding dogs that have congenital disorders is problematic, as this practice continues the disease in future offspring. Most breeders monitor the health of litters they have sold, in order to detect the emergence of congenital disorders such as this in litters or breeding stock. Therefore, it is critical that the history and health records of potential breeding pairs are obtained and examined before a puppy at risk of conditions such as this are purchased. There is evidence that Yorkshire Terriers and Bedlington Terriers are overrepresented when compared to reference populations of dogs (Westermeyer et al, 2009).

Drug and anesthesia induced decreases in tear production: Certain drugs/anesthetics can produce either temporary or permanent KCS. A decrease in tear production for up to 24 hours is sometimes noted to occur after anesthesia and surgery, but the inciting cause is unknown. Consequently, it is important for all veterinarians to use a lubricating ointment or fluid to protect eyes during surgery to prevent this temporary decrease in tear production.

There are other drugs whose use have been associated with the development of KCS. These include some of the sulfonamide antibiotics and etodolac, an orally administered nonsteroidal anti-inflammatory drugs that has been used to help relieve pain and inflammation in dogs with osteoarthritis (Klauss et al, 2007). In the latter study, dogs that had received the drug for less than 6 months had a much better chance to complete remission of clinical signs. The investigators advised veterinarians to monitor tear production before and during administration of this drug to ensure that problems can be identified early and drug administration discontinued, if necessary.

Iatrogenic KCS: The term 'iatrogenic' refers to a problem that develops as a result of or associated with a treatment. Consider, for example, a dog that has an abnormal growth involving the gland of the third eyelid (nictitans gland). If this abnormal growth were removed, it could increase the risk that the dog will develop KCS, because that gland is responsible for production of part of the tear film. In fact, this is what happened years ago when a condition caused by inflammation and proliferation of lymphoid tissue near the third eyelid (i.e., "Cherry Eye") was treated by removal the gland. Today, this condition is treated using a combination of medical and surgical treatments instead of removal.

Infectious Diseases: A common viral disease in dogs, canine distemper, is often associated with KCS. Canine distemper is a highly contagious disease that is typically spread via aerosolized respiratory secretions. In most cases, the virus first attacks the

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respiratory system, and then spreads to the gastrointestinal and nervous systems. When the virus colonizes components of the eye, including the cornea, conjunctiva and the lacrimal glands, KCS can develop (Gilger, 2009). Consequently, it is extremely important to have all dogs vaccinated against the canine distemper virus.

Metabolic Diseases/Disorders: Tear production has been reported to be reduced in a small number of patients being evaluated for endocrine abnormalities commonly encountered in dogs (Williams et al, 2007). These three conditions were hypothyroidism, diabetes mellitus and hyperadrenocorticism (Cushing's disease). Although the underlying cause or causes for the reduction in tear production were not identified in that clinical study, the investigators suggested that tear production should be measured in dogs with any of these conditions to reduce the chances the damage to the cornea could occur.

Neurologic: Parasympathetic innervation to the lacrimal glands is provided by one of the 12 cranial nerves, namely the facial nerve. Damage to this nerve, either due to disease or trauma, can result in KCS by decreasing the amount of tear film produced. Similarly, damage to the ophthalmic branch of the trigeminal nerve could result in loss of innervation to the lacrimal gland, conjunctiva, and upper eyelids, with the end result being the development of KCS.

How is Keratoconjunctivitis sicca diagnosed?

Dogs with KCS are often presented to the veterinarian because they have red/irritated eyes, are pawing at their eyes because they itch and/or hurt, and may have a thick ocular discharge that can range from off-white to green in color. The veterinarian also may notice that the third eyelid is protruded, and that the cornea no longer has its normal shiny appearance (**Figure 8.4**). This latter finding is due to inflammation of the cornea. In advanced cases of disease, there may be evidence of corneal ulceration and pigmentation; corneal scarring may lead to vision loss.

To differentiate KCS from other ocular disorders, the veterinarian will do a comprehensive eye exam that will include a Schirmer tear test, staining of the cornea with fluorescein dye, and evaluation of pressures within the eye for evidence of glaucoma.

Schirmer Tear Test: The Schirmer tear test is a painless diagnostic procedure designed to quantify the amount of tear film produced by the eye. To perform this test, the veterinarian places a thin strip of paper (about an inch long and quarter of an inch wide) just under the dog's eyelid for one minute. This piece of paper has a small scale on it **(Figure 8.5).** During the minute, the tear film "wicks" up the paper. At the end of one minute, tear production is quantified by measuring the distance the tear film travelled in the paper. The result is reported in mm/min, with values for normal dogs being >15 mm/min.

Application of Fluorescein Stain: Fluorescein is a bright yellow/orange stain that is used to detect corneal ulceration. The veterinarian will place a few drops of the stain in the eye, turn off the exam room lights, and use the ophthalmoscope to

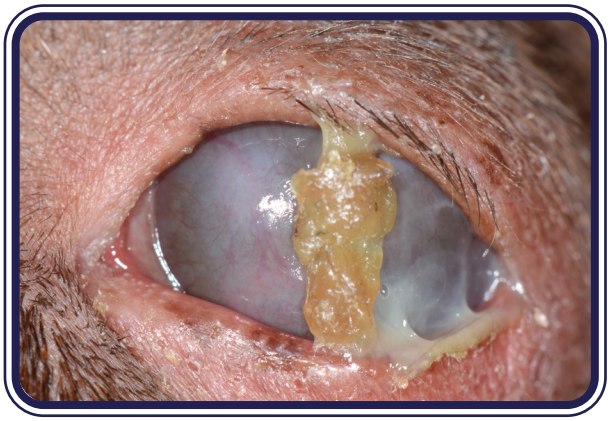

Figure 8.4 - An affected eye in a dog with keratoconjunctivitis sicca, characterized by a cloudy cornea and thick ocular discharge.

Figure 8.5 - A packet of standardized Shirmer Tear Test strips that are used to measure tear production.

Figure 8.6 - Examination of a dog's eye using a specialized ophthalmoscope.

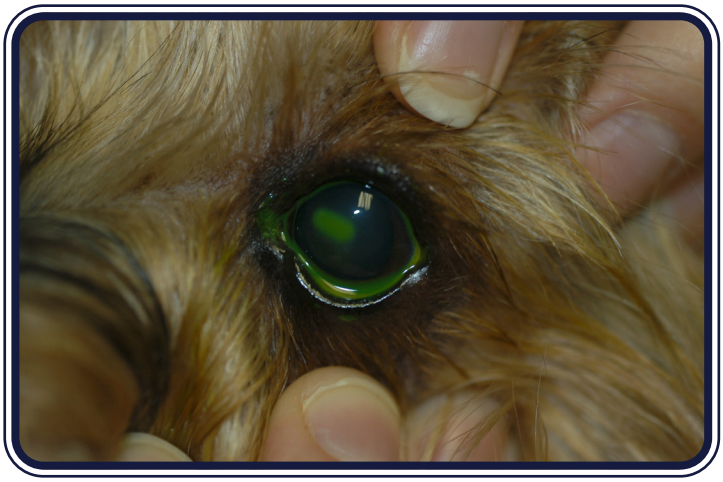

Figure 8.7 - The eye of a dog with keratoconjunctivitis sicca in which the green fluorescein stain identifies a damaged area of the cornea.

determine if corneal ulcers are present **(Figure 8.6)**. In dogs with KCS, it is not uncommon to also find corneal ulceration because of the chronic irritation (**Figure 8.7**).

Examination of Intraocular Pressure: Although changes in intraocular pressure generally do not occur in dogs with KCS, most veterinarians will measure intraocular pressure to rule out another relatively common eye disease, namely glaucoma. Measurement of intraocular pressure is performed in a quick, painless manner using a special handheld device known as a tonometer. Normal intraocular pressure in dogs ranges from 15 to 25 mmHg.

Treatment of Keratoconjunctivitis sicca

There are a variety of treatments for KCS that can be used. These include stimulating the production of tears, replacing the tears, reducing inflammation and controlling bacterial infections. For most dogs with KCS, topical treatments will be required for the life of the animal. Initially, application of topical medications to the eye can be challenging, as some dogs with KCS are painful. Fortunately, with effective management, the level of pain decreases and putting medications in the eyes becomes a routine practice for both dog and owner. Providing rewards as positive reinforcement may help. The following guidelines for deciding when to initiate therapy appear to be reasonable (Best, 2014):

1. Initiate therapy for KCS in all dogs presented with clinical signs of the disease and Schirmer tear test results <5 mm/min.
2. Either initiate therapy for KCS or repeat the Schirmer tear test in one month in breeds predisposed to the disease that have clinical signs of the disease and Schirmer tear test results of 10-15 mm/min.
3. Consider other causes for reduced tear production in dogs presented with clinical signs of the disease and normal Schirmer tear test results.

Stimulating Tear Production: Three drugs are commonly used in an effort to restore tear production in dogs with KCS. Two of these compounds, cyclosporine A and tacrolimus, modulate the immune response that appears to be responsible for the condition in a large number of dogs. They also reduce inflammation, restore production of mucin by goblet cells, and stimulate tear production. These drugs appear to be very effective, positive responses being reported for more than 80% of affected animals (Kaswan et al, 1990; Hendrix et al, 2011). The third compound, pilocarpine, stimulates tear production by interacting with receptors in the lacrimal system. This drug is used when the cause of the condition is determined to be neurogenic in origin (i.e., damage to the nerves involved in tear production).

Replacing Tears: Tear replacement solutions are typically a combination of ingredients that replace one or more components of the tear film. There are three types of solutions, gels and ointments that are used for this purpose. These include artificial tear solutions that help remove debris and mucus from the surface of the eye. Artificial tear solutions have a relatively short duration of activity, must be reapplied several times a day and are not effective as the sole treatment. Another approach is to use cellulose-based solution and gels that are thicker, last longer and can be applied less often. The most viscous formations, which include lanolin, mineral oil or petrolatum, are used most often for dogs that produce tear film deficient in lipids.

Topical Anti-Bacterial and Anti-Inflammatory Drugs: In some affected animals, there may be a secondary bacterial infection causing the thick, mucopurulent discharge. In

these cases, topical ophthalmic anti-bacterial drugs will need to be applied to the eyes 3-4 times daily. These drugs typically include a combination of bacitracin, neomycin and polymyxin. If the conjunctiva are inflamed, many veterinarians also will use topic corticosteroids, such as prednisolone or dexamethasone, to reduce the inflammation. These medications are manufactured as ointments and solutions; your veterinarian will determine which medication is best for your dog.

Surgical Intervention (Parotid Duct Transposition): Some dogs with severe KCS that is unresponsive to medical therapy, may require surgery. To understand the rationale for the surgical procedure used, it first is important to know a bit about the parotid salivary gland that is located behind the jaw and just below the base of the ear. This is the largest salivary gland in the body and produces secretions that aid in chewing and lubricating food and swallowing. Because tears and saliva share similar properties, saliva can be used successfully to treat dogs with severe KCS. The surgical procedure that is performed moves the duct that normally connects the gland with the mouth to a position near the conjunctiva (**Figure 8.8**). When this is done, the lubricating and antibacterial secretions from the salivary gland flow onto the surface of the eye. This flow of saliva is intermittent, and increases in response to eating. Veterinarians with experience performing this procedure routinely are most likely to have a successful outcome.

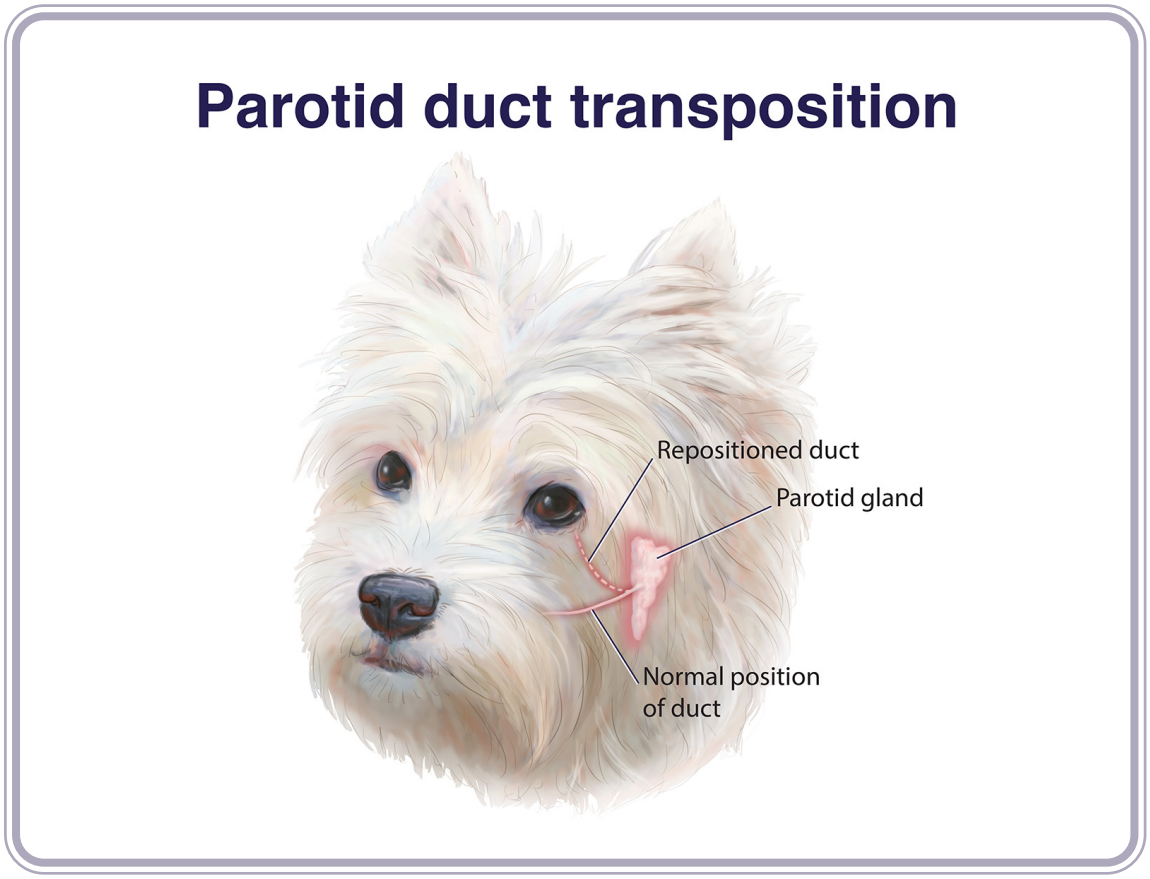

Figure 8.8 - An illustration depicting the normal position of the parotid duct where it enters the mouth and its new location adjacent to the eye after the parotid duct transposition surgery has been performed.

Current Research About Keratoconjunctivitis sicca

Galley AP, Beltran E, Pont RT. Neurogenic keratoconjunctivitis sicca in 34 dogs: A case series. Vet Ophthalmol 2022 Mar;25(2):140-152.

This study was performed to describe the clinical findings, imaging features, underlying conditions, treatment, and progression of 34 dogs presented between 2010 and 2019 with neurogenic keratoconjunctivitis sicca. The mean age at presentation was 8.2 years, 20 dogs were male, and 14 dogs were female. Treatment for neurogenic keratoconjunctivitis sicca was initiated in 88% of the dogs and included oral pilocarpine 2% and lacrimostimulant (n = 19), oral pilocarpine 2% only (n = 3), or lacrimostimulant only (n = 8). Eleven cases with follow-up were responsive (48%) with resolution of the clinical signs in a median time 4 months; all were treated with oral pilocarpine (± lacrimostimulant).

Bercovitz GR, Gaerig AM, Conway ED et al. Long-lasting otic medications may be a rare cause of neurogenic keratoconjunctivitis sicca in dogs. J Am Vet Med Assoc 2022 Nov 8;261(1):97-103.

This study was performed to characterize the clinical course and long-term prognosis of a suspected novel cause of neurogenic keratoconjunctivitis sicca secondary to florfenicol, terbinafine hydrochloride, mometasone furoate or florfenicol, terbinafine, betamethasone acetate. A retrospective analysis of medical records of 29 dogs that had onset of clinical signs of neurogenic keratoconjunctivitis sicca and reduced tear production within 1 day after application of otitis externa medications containing terbinafine and florfenicol. A corneal ulcer was diagnosed in 68% of the dogs. Fortunately, affected dogs had a good prognosis for return of normal tear production within 1 year.

O'Neill DG, Brodbelt DC, Keddy A et al. Keratoconjunctivitis sicca in dogs under primary veterinary care in the UK: an epidemiological study. J Small Anim Pract 2021 Aug;62(8):636-645.

This study was performed to estimate the frequency and breed-related risk factors for keratoconjunctivitis sicca in dogs in the UK under primary veterinary care. There were 1456 keratoconjunctivitis sicca cases overall from 363,898 dogs (0.40%). Compared with crossbreds, breeds with the highest odds ratio for keratoconjunctivitis sicca included American cocker spaniel, English bulldog, pug and Lhasa apso. Conversely, Labrador retrievers and border collies had reduced odds. Brachycephalic dogs had 3.6 times odds compared to mesocephalics. Advancing age was strongly associated with increased odds. Based on these findings, quantitative tear tests are recommended during yearly health examinations for breeds with evidence of predisposition to keratoconjunctivitis sicca. Breed predisposition to the condition suggests that breeding strategies could aim to reduce extremes of facial conformation.

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