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Canine Keratoconjunctivitis Sicca: Current Concepts in Diagnosis and Treatment

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Abstract

Keratoconjunctivitis sicca or dry eye is a commonly recognised condition of canine patients in veterinary practice. The majority of cases are seen in a number of pedigree dog breeds from West Highland White terriers, English and American Cocker Spaniels, Cavalier King Charles spaniels, Lhasa Apsos and Shuh Tzus among a number of other breeds. In these animals an immune-mediated destruction of the lacrimal gland appears to be taking place and topical cyclosporine has, for many years, been a valuable treatment option in these animals. Other causes of dry eye are neurological dysfunction and drug-related lacrimotoxicity. In these cases topical cyclosporine is not effective and treatment with tear replacement drops is required. Another option is parotid duct transposition which can give a lasting improvement in ocular surface pathology. Diagnosis of canine dry eye is primarily by use of the Schirmer tear test, in which tear strip wetting of 15-20mm/min is normal and a wetting of less than 10mm/min is characteristic of dry eye. Other diagnostic modalities such as staining with the vital dye Rose Bengal, determination of tear ferning or measurement of tear film breakup time or tear film osmolarity are used to varying degrees by those investigating the canine tear film but in clinical practice the Schirmer tear test remains the key diagnostic test. Understanding the pathogenesis and treatment of canine keratoconjunctivitis sicca is important for the animals thus affected, but also in the manner it provides a useful spontaneous model for dry eye in human patients. Other models include rodents with inherited predisposition to dry eye and those in which a continual airflow dries the ocular surface, but the spontaneous canine model has the advantage of an eye much more similar in size to the human eye than is the mouse or rat globe and an outbred species living in the same environment as the human patients.

Keywords: *Dog; Eye; Tearfilm; Dry Eye; Keratoconjunctivitis Sicca; Keratoconjunctivitis Sicca (KCS); Ophthalmic Disease; Schirmer Tear Test (STT)*

Introduction

In a recent audit of one thousand dogs referred to my clinic for ophthalmic disease, a full 182 animals had a reduction in their aqueous tear production either as a primary problem or as a key contributory factor in the pathogenesis of the ocular defects observed [1]. If this proportion of cases truly reflects the prevalence of dry eye in the canine population, and I consider it probably does, keratoconjunctivitis sicca is an important condition that needs to be foremost in clinicians' minds when examining dogs with ocular conditions. What are the current diagnostic tests and treatment regimens for dealing with animals with tear film deficiencies?

Prevalence of dry eye

The prime position of keratoconjunctivitis sicca (KCS) in my survey of one thousand dogs does indeed reflect the high prevalence of the condition in canine patients. The first survey of dry eye was undertaken by Professor Lloyd Helper, a key player at the very beginning of veterinary ophthalmology, who published this first report on the condition in dogs in 1976 [2]. He noted only 0.4% of the canine population to be affected with a deficiency in tear production, but twenty years on Dr Renee Kaswan, a leader in dry eye research, reported a prevalence of up to 35% in the patients she surveyed in 1998 [3]. The truth is that the number of animals affected is probably somewhere in between these two figures. Research we undertook in Cambridge to measure the Schirmer tear test (STT) in one thousand dogs with apparently normal eyes demonstrated levels of tear production lower than 15mm of tear strip wetting in one minute

in 131 dogs giving a prevalence of 13%, but that was in apparently normal dogs. We will consider the tests for canine KCS later in this review but first perhaps we should note a philosophical issue in defining disease prevalence. The problem with trying to obtain a true prevalence of clinical dry eye in the whole dog population is that as veterinarians we will see many dogs with KCS, but we cannot be sure of the number of animals in the whole population from what these dogs were taken. But even if the KCS prevalence were only a little more than 1% of the canine population, that is still a large number of dogs in every veterinary practice. It shows the importance of being aware of dry eye in every dog that is presented with a red eye or a corneal ulcer, both of which conditions may well be associated with KCS.

The biology of the tear film in health and disease

For many years the tear film was considered to be a trilaminar structure with a deep layer of mucins attached to the superficial epithelium, a middle and major layer of aqueous tears and then a superficial layer of lipid which prevents aqueous tear evaporation [4]. Work further evaluating the tear-film by laser interferometry shows that some mucins are attached to the epithelial cell membranes while others are liberated into the aqueous layer and that the entire tear-film is considerable thicker than previously thought at xum for the human tear film; sadly similar measurements have not be attempted for the canine patient [5]. Evaluation of the lipid layer uses polarised light bio microscopy to determine both the distribution and the thickness of the lipid layer [6].

The aqueous later of the tear film is produced, in the dog, by the lacrimal gland and the gland of the nictitating membrane, also termed the nictitans gland. Studies removing the latter gland have suggested that around 30% of the aqueous tear production rises from the nictitans gland [7]. The general view of veterinary ophthalmologists is that for this reason removal of the nictitans gland in cases of prolapse for instance, is strongly to be discouraged. This is however based on one paper by Dr Rhea Morgan who developed the very valuable pocket technique for replacement of the gland in such cases [8]. She showed that in dogs where the gland had been removed there were a significantly higher proportion of cases of KCS seven years after surgery but not before. Years before Dr Lloyd Helper had experimentally excised nictitans glands and or lacrimal glands for dogs and shown KCS to occur only when both glands were removed.7 Subsequent studies on epithelial cell pathology following nictitans gland removal have similarly not noted substantial effects [9]. A potential confounding effect here is that breeds predisposed to nictitans gland prolapse are also predisposed to KCS. This itself is an important factor in recommending replacement of the gland. If KCS does occur having as much remaining lacrimal tissue on which cyclosporine can have its beneficial effects will be critical to retaining ocular surface health.

The key signs of canine KCS when it has reached a clinical stage by which it will be affecting the animal are a dull lustreless ocular surface and importantly a reflection of a penlight when directed at the cornea which does not have a sharp boundary but rather is broken up into many small individual reflections. A normal uninterrupted tear film over the cornea surface gives a crystal clear reflection. Other signs include conjunctival redness and a mucoid to muco-purulent ocular discharge. The redness signals conjunctivitis so is seen not only on the globe itself but also on the conjunctiva of the lid. Many clinicians fail to reflect the upper conjunctiva when examining the eye. The lower conjunctival sac can be hyperaemic just because of debris moving into it from the ocular surface so even though it is a lot easily to pull down the lower lid and examine the lower conjuctival sac; it is always worth assessing the upper conjunctiva by gently pulling back the upper lid. This can be important in differentiating conjunctivitis from another inflammatory disease resulting in red eye: uveitis. Conjunctivitis will involve the conjunctiva of both the globe and the lid, while the intraocular inflammation of uveitis will give a hyperaemia of the episclera overlying the globe alone and indeed particularly just behind the limbus where the cornea meets the sclera, since this area overlies the ciliary body, this redness known as ciliary flush. The other important feature to note about ocular redness resulting from inflammation whether conjunctivitis or uveitis is that the hyperaemia is a diffuse redness - it comes from cytokines percolating through the sclera and episclera from the ciliary body or in the conjunctiva itself in conjunctivitis, while in glaucoma the redness comes from vascular congestion of the episcleral vessels and so in ocular hypertension the sclera between engorged episcleral vessels is white.

The ocular discharge which is often seen in KCS might suggest that a bacterial infection is responsible for the ocular signs, and many cases of dry eye are treated with antibiotics unsuccessfully after another before a Schirmer tear test identifies the underlying problem of KCS. Most eyes with deficient tear production are no more infected with bacteria than are eyes with normal tear production [10]. A bacteriology swab may yield a spare growth of Gram positive cocci such as Staphyloccus and Streptococcis but these are normal comensal of the ocular surface and should not be taken as of pathological signficance unless in a profuse growth.. This lack of signficant infection may surprising since a number of anti-bacterial factors exist in tears. One of these is lactoferrin [11]. Bacteria need iron as a key

part of their electron transfer chain - just as in mitochondria which are of course intracellular bacteria of a sort. Iron is thus of critical importance for bacteria on the ocular surface and if infection is going to progress a ready supply of iron is critical. The mucosal surface of the eye responds by producing lactoferrin to bind as much iron in the tear film as possible. Another key antibacterial agent in tears is the antibody dimer secreted at al mucosal surfaces, immunoglobulin a which agglutinates pathogens and thus inactivates them. Also in the normal tear film is lysozyme, an enzyme hydrolysing N-acetylmuramic acid - N-acetyl-D-glucosamine linkages in peptidoglycans which are the key buiding blocks of Gram positive bacterial cell walls [12]. We might then find it surprising that KCS-affected dogs do not seem to be particularly affected by ocular surface infections. We have not discussed toll like recptors, a key part of the primitive innate immune system which may be central to protecting the ocular surface. Whatever the case, it is vital to maintain the tear film since it is so critical in maintaining the health of the ocular surface and thus any dog with a red eye or a mucoid or mucopurulent ocular discharge should have a Schirmer tear test as a key part of its ophthalmic investigations.

A key point is that dogs with KCS should be caught at an early stage before the ocular changes resulting from dry eye have irreversible effects. So what factors are important in the genesis of KCS which might show that the disease is in its preclinical phase before causing ocular surface pathology?

The pathology of KCS

Discussion of the pathology of dry eye should be divided into evaluation first of the pathogenesis of the lacrinal gland damage which reduces tear production and secondly the pathology of the ocular surface when deprived of the covering of the tear film. In dogs, as in people with Sjorgren's syndrome where KCS occurs concurrent with xerostomia, dry mouth, and rheuamtological pathology, the lacrimal gland is infiltrated by a predominantly CD3+ T cell lymphocytic population. We evaluated nictitans glands excised from dogs with KCS in which parotid duct transposition was being performed and showed by immunohistochemistry that 71% of inflammatory cells in idiopathic KCS-affected dogs were CD3+ lymphocytes while 28% were CD79a+ B lymphocytes. Antibodies directed against canine CD4 and CD8 antigens which would work in formalin fixed tissues were unfortunately not available at the time of undertaking that study. It might be argued that the inflammatory cell infiltrate is a result rather than a cause of the dry eye symptoms but in dogs with neurological dry eye where the cause of reduced tear production is neurological dysfunction [13]. The relevant proportions of CD3+ and CD79a+ cells were 42% and 58% with a predominance of B cells. The inflammatory cell populations of the normal nicitating membrane lacrimal gland were 44% and 56% respectively. It would thus appear that what has been known as idiopathic canine KCS is indeed a T cell-predominating immune-mediated, one might say autoimmune disease.

Other causes of KCS include the distemper virus, Toxoplasmosis and Leishmaniasis while there are genetic influences which yield cases such as Cavalier King Charles spaniels with congenital KCS and dermal ichthiosis, quite apart from the breed predispositions of idiopathic dry eye in West Highland White terriers, Cocker spaniels, Shih Tzus and Lhasa Apsos [14-17]. Neurological dry eye gives a lack of tear production because of defective neural stimulation of tear production, but in all these different causes of tear efficiency similar effects are occurring on the ocular surface. What then of the pathology of the ocular surface in the face of tear film deficiency? Severe KCS engenders corneal vascularisation, pigmentary keratitis and in some cases corneal ulceration. Without adequate lubrication the structural integrity and transparency of the cornea is all too easily lost. It is vitally important to be able to assess tear production before such changes can become permanent, so to tests of tear production we now turn.

Tests of tear production

In the dog the classic test of tear production has since 1975 been the Schirmer tear test (STT), first devised by Otto Schirmer in 1903 and consisting of measuring the tear uptake by a standardised filter paper strip over one minute [18]. In fact the fluid taken up by the filter come not only from tears produced de novo but also those already in the tear lake. We have differentiated these by plotting the STT value over time, showing an initial rapid uptake over around the first 20 seconds and then a more gradual increase, this being the de novo tears of production [19]. The normal level of tear production in the dog used to be defined as 10-20mm/min but more recent studies have suggested that dogs with STT results of 15-20mm/min are normal while those between 10and 15mm/min may constitute a sub-clinically dry group. Our research has shown an average STT of one thousand dogs with normal eyes of 18.6mm/min but different breeds have significantly different STT values. Interesting a number of breeds classically recognised as predisposed to KCS, namely the West Highland white terrier, the American and English Cocker Spaniel, the Lhasa Apo, Shih Tzu and Cavalier King Charles Spaniel have significantly lower STT results. In human patients the STT is much less valuable

as a clinical determinant of ocular surface pathology and a number of other tests are used, predominantly Rose Bengal staining (RBS), tear film break up time TFBUT), tear ferning and determination of tear film osmolality. While ophthalmologists use these techniques there is little data published on the TFBUT or degree of RBS in normal dogs or those with KCS of differing severities, rendering use of the techniques difficult in the assessment of cases of KCS.

Rose Bengal is a vital dye which used to be considered as binding to devitalised epithelium, but more recent work suggests that it highlights areas of mucin deficiency. Given this, it is clearly a measure of ocular surface pathology rather than lacrimal function and therefore well complements measures such as STT and TFBUT. Again in veterinary ophthalmology clinicians note changes in TFBUT but we have, as yet, no reports documenting figures in normal and KCS-affected dogs. The key feature assessed by the TFBUT is removal of tears by evaporation and nasolacrimal drainage. Particularly in brachycephalic breeds we can expect a significantly increased evaporative loss of tears from the central corneal surface and thus an evaporative dry eye even in the face of an apparently normal STT. Measuring TFBUT in these dogs would be a valuable project, given the prevalence of ocular surface pigmentation in breeds such as pugs and Pekingese where evaporative dry eye through excessive loss of fluid for the central tear film is probably a significant factor in the development of these pigmentary changes. TFBUT is classically determined by using fluorescein dye to facilitate visualisation of a 'hole' appearing in the central tear film, better to enable to time to break up of the tear film to occur. The problem with this technique is that by adding dye to the ocular surface one is to some extent altering the physiology of the ocular surface. Here we have a classic example of Heisenberg's uncertainty principle. By the very fact of examining an electron, noted Heisenberg in his classic paper for 1927, one is altering its state, meaning that one cannot determine the position and speed of the electron concurrently as by examining one you will be changing the other. Physicists have argued that this is a particular effect of the quantum world where objects examined such as electrons can be significantly influenced by the photons used to examine them. But just the same could be said of fluorescein dye in a drop or on a Fluoret changing the tear film we are trying to examine. What is needed is a method of examining the tear film surface which has no effect on it. The Keeler Tearscope provides just such a device whereby a grid of lines is projected onto the ocular surface facilitating determination of the point at which the tear-film develops a central evaporative hole when the lids are held open.

Another indirect measure of tear film evaporation is that of tear film osmolarity. If here is excessive evaporation of fluid form the ocular surface then the osmolarity of the tear film, the concentration of ions naturally present in it, will increase. This is important as excessive concentrations of ions in the tear film are thought to be important in the pathogenesis of ocular surface changes in the disease. The problem is that determining osmolarity using previous measures of freezing point depression required collecting a volume of 0.2ml of tear fluid. A more modern technique, the Tear lab, uses a disposable sampling tip with microchip it analyses the osmolarity of tears through their conductivity, providing an almost instantaneous reading in mOsm/L. In a recent, and as yet unpublished study, we found poor correlation between the mOsm/L reading and STT value but this might be expected since the STT reading is primarily evaluating volume of tears produced (both in the tear lake and produced de novo as we discussed above) while the osmolarity determination is assessing the effect of both tear production and tear evaporation on solute concentration in the tear film. There was a significantly higher osmolarity in the tears of brachycephalic breeds, strongly suggesting that excessive tear-film evaporation does have an effect on the ocular surface in these dogs.

A completely different method of evaluating what is probably the concentration of solutes in a teardrop is tear ferning. A drop of tear fluid obtained at the medial canthus with a microhaemtocrit tube is allowed to dry on a microscope slide held at a defined temperature and humidity under a microscope and the resulting crystallisation of the solutes is observed. In a normal dog this produces a strikingly beautiful pattern of ferning covering the entire face of the drop. Such an effect occurs in all body fluids and was first noted in cervical mucus by Papanicolou. In animals with progressively more severe KCS the crystals become smaller than less frond-like. As the osmolarity readings there is poor correlation with the STT value since this test is in all probability evaluating a completely different feature of the rear film both in normality and in disease.

Restoring Tear Production

In the 1980s Dr Renee Kaswan of Georgia veterinary school was talking to a friend who had recently received a renal transplant. He complained of an unusual feeling in his eyes and, since Dr Kaswan already had a significant interest in tear production, she uses the STT to evaluate his tear production. Finding it substantially increased form the normal level, she surmised that, given the similarity of the lymphocytic infiltrate in the lacrimal gland in KCS and the kidney in renal transplant failure and the ameliorative action of cyclosporine in the latter disease, topical cyclosporine might be valuable in dogs with KCS. Having a group of dogs with the condition she and Dr MA Salisbury evaluated the

drug and found it hugely successful in restoring tear production in these dry eyes [20]. Cyclosporine is a highly lipophilic drug which accounts, pharmacokinetic terms, for why it concentrates so well in the lacrimal tissue but does mean that it needs to be given topically in a lipid vehicle, originally olive or corn oil. Kaswan and Salisbury chose a concentration of 2% but subsequently others reported equivalent lacrimogenic activity at half that concentration and I used it at only a tenth of the concentration with equally beneficial results [21]. The drug works at between 0.2 and 2% in around 90% of cases of idiopathic canine KCS while at lower concentrations it appears to produce effective tearing in those cases in which it works, but this becomes a progressively lower proportion of cases. For cases where continual topical medication is difficult episcleral cyclosporine implants have recent.y been developed which may be highly valuable [22].

It is generally considered that cyclosporine has its lacrimogenic activities through its immunomodulatory effects, reducing or preventing cytokine production by lymphocytes via its interaction with the cytoplasmic protein calcineurin. We have shown, however, that cyclosporine significantly increases tear production in dogs with normal tear production so perhaps there is another mechanism through which is effects tear production. We know that neural input is needed to see a lacrimostimulatory effect of topical cyclosporine. Dogs with neurogenic dry eye, characterised by a dry nostril on the ipsilateral side of the face as the dry eye, since the facial neurons innervating the lacrimal gland also supply the media nasal gland which provides moisture to the external nares, do not generally respond to topical cyclosporine [23]. One paper dissecting the lacrimal response to cyclospoirne in mice has reported that the mechanism of action involves effects of the drug on neurotransmitter release at the lacrimal acini [24]. There is much more to do in dissecting the mechanisms both pathological and therapeutic in dry eye but perhaps sometimes we have to go back to the old ways of using tear replacement drops in unresponsive dry eye, be it in human or canine patients.

Replacing the tear film

As we have noted dogs with neurogenic KCS and perhaps 5% of idiopathic presumed autoimmune cases do not respond to 0.2% cyclosporine. A number of these do produce an adequate tear film with more concentrated cyclosporine or with similar drugs such as tacrolimus or pimecrolimus although it is unclear exactly what proportion of 0.2% cyclosporine resistant cases respond to these other immunomdulatory drugs [25-27]. Some neurogenic cases, again as noted above, respond to oral pilocarpine without experiencing noxious side effects but an annoyingly stubborn if small proportion of cases fail to respond to any medical management attempting to restore normal tear production. With these animals we are forced back to the methods used in the pre-cyclosporine days before the late 1980s, that is to say the surgical technique of parotid duct transposition (PDT) or medical tear replacement.

For many years PDT was widely used and considered generally successful probably moreso in dogs than in people, though recent advances in the surgical transposition o gland and duct with it blood supply and innervation has brought use of saliva in tear replacement back to the fore in human ophthalmology. It has to be remembered that both saliva and tears are transudates of serum and contain similar levels of electrolytes crucial to the beneficial actions of the tear film on the ocular surface as noted above. Clearly saliva also contains enzymes such as amylase and is regulated in an entirely different manner from the factors that stimulate tear production. Some animals with a positive result from the perspective of volue of saliva replacing tears will fail because of calcium deposition in the ocular surface with subsequent reduction in clarity of vision and probably more importantly profound irritation from the crystalline deposit on the ocular surface. Treatments here can include chelation of the calcium with topical EDTA. The side effect of excess tear production with a moist dermatitis on the facial skin below the eye by an overly successful PDT procedure can be difficult to remedy and a proportion of procedures will fail with the eye returning to a dry state because of cicatrisation of the duct.

Recalling the pre-cyclosporine days when tear replacement was the order of the day in most KCS cases, the key thing to remember then was that each animal responded differently to the various tear replacements. Some would react well to carboxymethylcellulose while in others ocular surface health was better restored with drops containing polyvinyl alchohol. Yet others seemed best treated with lacrilube though the sheep lanolin product was probably best retained for use last thing at night given its considerable effect on vision through blurring the visual axis. The very fact that many tear replacements needed to be tried suggests that nothing worked particularly well. Today we have gels containing carbomers and hyaluronic acid but again different dogs seem to respond in varying degrees to the wide variety of products available. One new product which in our hands at least seems to provide a particularly efficacious tear replacement in each canine KCS patient in which we have tried it, is a cross-linked hyaluronic acid gel, Remend (Bayer, Newbury) [28]. It may not have struck you before but the eye is very much like the hip joint. Both are ball and socket joints with the sclera of the eye equating to the cartilage of the joint, the conjunctiva equivalent to the synovial

membrane and the only difference being that instead of a femur emerging for between the eyelids there is a corneal surface. The fact that the eye moves around and sees while the hip only has to move, means that tears cannot contain the hyaluronic acid (HA) that makes joint fluid so viscous. It is did our vision would be blurred in the extreme. HA can exist at different molecular weights, these corresponding to different lengths of the polymer of D-glucuronic acid and D-N-acetylglucosamine . We have previously shown that an HA containing tear drop, Clinadry was superior in efficacy to the carbomer gel which is widely used in canine ophthalmology [29]. We noted above that the tear film mucins are partially attached to the membranes of the most superficial epithelial cells and partially free floating in the aqueous layer of the tear film. A molecule which aspires to emulate such a natural ocular surface moiety should do just the same. This HA achieves. HA in solution has a non-Newtonian rheology. That is to say that as the long chain molecules interact in solution they tangle together and the flow characteristics are very different form a fluid with smaller molecules such as polyvinyl alchohol or carboxymethylcellulose. This is extenuated in Remend in which the HA molecules are not merely interacting electrostatically but covalently bonded together making a much more viscous gel. In a recent masked study comparing Remend and a standard HA tear replacement drop, we showed that dry eye symptoms of conjunctival hyperaemia, ocular irritation and ocular discharge were all reduced significantly more with the cross-lined HA polymer Remend than with the more conventional HA drop, as shown in figure x which compares the ameiorative actions of Remend and a standard HA tear replacement drop [30]. The other advantage of using an HA product is that the molecule has fascinating effects on epithelial cell and fibroblast migration through its binding of the cell surface receptor CD44. Thus the HA in Remend acts both as a physical supportive matrix and also as a depot for HA monomers to be released with effects on cell activation and migration.

Surgical Approaches to Canine Dry Eye

In the days before the lacrimogenic effects of topical cyclosporine were recognised, a key technique for restoring ocular surface health was surgical transposition of the parotid salivary duct into the ventral conjunctival sac. Saliva and tears are both ultra-filtrates of plasma and thus the parotid duct transposition might seem the ideal solution to dry eye [31]. The only problem is that post-surgical complications are common, the two most common being over-production of saliva with resultant epiphora and moist dermatitis, and deposition of calcium crystals on the ocular surface. Over-production can be remedied with a second surgery to reduce the calibre of the duct by suturing it part closed, although this can reduce saliva production to the point where the ocular surface is not sufficiently supplied with lubricating saliva [32]. The issue of calcium deposition can be more taxing to address. Topical EDTA drops can chelate the excess calcium while milk replacer powder has been anecdotally reported to reduce crystal formation on the ocular surface.

Conclusion

And so maybe we should leave it there: Continually developing treatments for a continuing problem, yet with more issues rearing their ugly heads all the time. Surgical treatments which use saliva for tears but not without complications. Tear replacement drops which have, truth to tell, improved through the years but still need very regular application. Topical cyclosporine therapy however, which was revolutionary and took more than a quarter of a century to be translated to a successful treatment for dry eye in the human patient. Dry eye then a significant problem in both dogs and people and perhaps the best opportunity for translational medicine where advances in diagnosis and treatment in one species can readily be translated to the other, with care to take note of differences between the two of course. Maybe we need to take more lessons from dry eye to see how better we can use canine conditions as spontaneous modes for human diseases at the same time as improving treatment regimes for the animals themselves.

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