How study of naturally occurring ocular disease in animals improves ocular health globally

Brian C. Gilger, DVM, MS, DACVO, DABT*

Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC

*Corresponding author: Dr. Gilger (bgilger@ncsu.edu)
doi.org/10.2460/javma.22.08.0383

ABSTRACT
In this article, which is part of the Currents in One Health series, the role of naturally occurring ocular disease in animals is reviewed with emphasis on how the understanding of these ocular diseases contributes to one health initiatives, particularly the pathogenesis and treatment of ocular diseases common to animals and humans. Animals spontaneously develop ocular diseases that closely mimic those in humans, especially dry eye disease, herpes virus infection (cats), fungal keratitis (horses), bacterial keratoconjunctivitis, uveitis, and glaucoma. Both uveitis and glaucoma are common in domestic animals and humans, and many similarities exist in pathogenesis, genetics, and response to therapy. Furthermore, the study of inherited retinal disease in animals has particularly epitomized the one health concept, specifically the collaborative efforts of multiple disciplines working to attain optimal health for people and animals. Through this study of retinal disease in dogs, innovative therapies such as gene therapy have been developed. A unique opportunity exists to study ocular disease in shared environments to better understand the interplay between the environment, genetics, and ocular disease in both animals and humans. The companion Currents in One Health by Gilger, AJVR, December 2022, addresses in more detail recent studies of noninfectious immune-mediated animal ocular disease and their role in advancing ocular health globally.

As many veterinary practitioners have experienced, ocular disease is common in animals. Plus, there are many similarities between the ocular diseases in companion veterinary species and those in humans. Study of naturally occurring ocular diseases in animals by veterinarians is particularly important in one health initiatives, where optimal health outcomes are achieved by recognizing the interconnection between people, animals, plants, and their shared environment.1,2 The CDC defines one health as the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and our environment.3 In ophthalmology, the study and sharing of information by veterinary practitioners are particularly important to advance knowledge of pathogenesis and treatment of common ocular diseases, such as dry eye, keratitis, uveitis, glaucoma, and retinal degeneration. Who better than veterinarians to study these naturally occurring ocular diseases in animals and to translate these observations to improve health in animals and humans? This article, which is part of the Currents in One Health series, reviews the importance of understanding eye disease and the development of advanced therapeutics through the study of naturally occurring ocular diseases in animals. The companion Currents in One Health manuscript by Gilger, AJVR, December 2022, addresses in more detail recent studies of immune-mediated naturally occurring animal ocular disease and their role in advancing ocular health. Ocular diseases that are common in both animals and humans are reviewed herein with an emphasis on their one health perspective.

Dry Eye Disease

Dry eye disease (DED) or keratoconjunctivitis sicca is very common in domestic animals, particularly dogs. DED is ocular surface inflammation resulting from a decrease in aqueous tear production or a reduction in other tear components (Figure 1). The normal tear film is critically important for ocular surface health, as it provides nutrition, lubrication, and immune homeostasis as a major component of the innate immune barrier of the eye. Without normal tears, chronic irritation and microbial overgrowth may occur due to a reduction of antibacterial peptides and IgA in the tears.4 Dog breeds such as the American Cocker Spaniel and West Highland White Terrier may have a high prevalence of DED that is > 5%.5 Humans also suffer from DED with an estimated prevalence of > 11% in patients over the age of 50.6 In dogs and humans, clinical signs of DED are similar and include conjunctival redness, mucoid discharge, and irritation with chronicity, corneal scarring, and vascularization. Decreased vision and eventually blindness may develop unless effective treatment is initiated. Although the cause of DED is multifactorial
with substantial environmental influences (eg, lack of humidity, exposure to smoke), most DED cases in dogs and humans have an immune-mediated pathogenesis.\textsuperscript{4,6–8} Therefore, the study of DED in dogs is particularly important to generate new therapeutics. Over 30 years ago, Kaswan et al\textsuperscript{9} reported that topical ocular application of cyclosporine not only increased tear production in DED canines but also improved clinical signs associated with DED such as reduction of opacity, conjunctival hyperemia, and vascularization.\textsuperscript{9} These observations led to the global use of calcineurin inhibitors for the treatment of DED in dogs and humans (eg, the development of Restasis), and calcineurin inhibitors are now the leading treatment for DED in humans and dogs over the past 30 years.\textsuperscript{10} More recently, Murphy et al\textsuperscript{11} demonstrated efficacy in DED dogs of topical lifitegrast, a novel immunosuppressive small-molecule pharmaceutical that antagonizes lymphocyte function–associated antigen-1. These findings translated to the approval of Xiidra in July 2016 in the US for the treatment of DED in humans.

Study of this naturally occurring disease in dogs has led to a better understanding of the pathogenesis and development of new therapeutic approaches, such as the use of topical substance P and use of new antibiotics, such as tetracyclines.\textsuperscript{22,23} It was found recently that a gene defect in NOG gene in Boxers may increase their susceptibility to developing chronic superficial ulceration.\textsuperscript{20} The NOG gene encodes for the noggin protein, which plays a role in the proliferation of limbal stem cells that are responsible for epithelialization of corneal defects.\textsuperscript{20} Further study is needed on the role of noggin protein deficiency and corneal ulceration in dog breeds other than Boxers and in humans.

Dogs also develop spontaneous corneal endothelial cell dystrophies and degenerations. The genetic origin of these diseases in dogs is poorly understood; however, many of these conditions are similar clinically to Fuchs dystrophy and other endothelial dystrophies in humans.\textsuperscript{24} Therapeutic interventions to improve endothelial function, such as the use of the rho kinase inhibitor netarsudil in dogs with spontaneous endothelial dysfunction, may also benefit keratitis (horses)\textsuperscript{15}; and bacterial keratoconjunctivitis,\textsuperscript{14} which may develop in all species. Studies of new methods to control these infections in animals may pave the way for new treatment paradigms in humans. Examples include the use of ocular photodynamic therapy, atmospheric plasma therapy, new antibacterials, antifungals, and antivirals.\textsuperscript{15–17}

Nonhealing superficial corneal ulceration has many synonyms in animals and humans, including indolent ulcers, recurrent erosions, and superficial chronic nonhealing corneal epithelial defects.\textsuperscript{18–21} These lesions are common in dogs, horses, and humans and have very similar clinical features, namely chronic superficial corneal ulcers with loss of epithelium, redundant nonhealing epithelial edges, and a lack of causative infectious agents (Figure 2).
humans with Fuchs dystrophy. Work from the laboratory of Drs. Sara Thomasy and Brian Leonard is at the forefront in translating these novel treatments of canine corneal diseases to humans.

Although very rare, dogs and cats have been diagnosed with mucopolysaccharidosis (MPS), or lysosomal storage diseases, which are genetic disorders resulting from a defect in the enzymes to degrade polysaccharides, resulting in tissue accumulation of these sugars and subsequent pathology. In addition to numerous systemic health abnormalities, including heart disease and orthopedic and neurologic changes, storage diseases (ie, MPS 1, IIa, VI) may spontaneously develop ocular diseases, such as retinal degeneration, glaucoma, and corneal cloudiness (Figure 3). In addition to numerous systemic health abnormalities, including heart disease and orthopedic and neurologic changes, storage diseases (ie, MPS 1, IIa, VI) may spontaneously develop ocular diseases, such as retinal degeneration, glaucoma, and corneal cloudiness (Figure 3).

Naturally occurring MPS in dogs and cats have been instrumental in the understanding of pathogenesis of the disease and evaluating treatments, such as enzyme replacement therapy, hematopoietic bone marrow transplants, and gene therapy. Mucopolysaccharidoses I and VI cause blindness primarily through the development of corneal opacities, a result of the buildup of intra- and extracellular glycosaminoglycans. Recently, gene therapy to replace the missing α-L-iduronidase (IDUA) gene in MPS 1, or the arylsulfatase B (ARSB) gene in MPS VI, has been developed, and when delivered to the corneal stroma using an adeno-associated virus (AAV) vector, the corneal opacity rapidly clears. These promising therapies are being translated for treatment of these blinding disorders in humans.

Because of the anatomic similarity between animals’ corneas and humans, the study of naturally occurring infectious keratitis translates well to human diseases. Animals, including humans, share the propensity to develop infections after corneal injuries. Once infections develop, they induce severe inflammation, pain, and loss of vision. Study of pathogenesis of herpesvirus and fungal or bacterial keratitis is important to not only prevent blindness in animals but also provide an excellent one health opportunity to study the disease for humans. A great example is fungal keratitis, a disease that occurs in many animals, but the 2 most common species that are affected are horses and humans (Figure 4).

The pathogenic organisms (eg, Candida, Aspergillus, and Fusarium spp) are the most common causative pathogenic organisms in humans and horses. The study of disease pathogenesis, pathogenic organisms, and treatment of fungal keratitis translates between species. For example, a new antifungal, luliconazole, is effective against both equine and human fungal keratitis. Furthermore, advanced treatment of fungal keratitis, such as photodynamic therapy or cold atmospheric plasma treatment, is being evaluated in horses and humans fungal keratitis.

Uveitis

The uveal tract of the eye consists of the iris, ciliary body, and choroid. It is the vascular portion of the eye and is the primary site of the blood-ocular

Figure 3—Corneal opacity in feline mucopolysaccharidosis VI. Direct (A) and retroilluminated (B) images of a cat with mucopolysaccharidosis VI demonstrating diffuse corneal opacity manifesting as a “ground glass” appearance.

Figure 4—Fungal keratitis in a horse. This is a superficial corneal ulcer with a filamentous fungal infection caused by Aspergillus spp.
Following trauma or systemic inflammatory responses, the blood-ocular barrier can be disrupted allowing for the influx of inflammatory cells into the eye. The resulting inflammation is termed uveitis. Self-antigen recognition by infiltrating inflammatory cells, such as T lymphocytes, results in a further influx of inflammatory cells and prostaglandin release. This results in the typical clinical signs of uveitis, namely ocular pain, opacity to the aqueous and vitreous humor (ie, aqueous and vitreous flare), cellular influx, blood vessel swelling, and fibrin formation (Figure 5).

Chronically, uveitis may cause cataract formation, retinal detachment, and retinal degeneration. Uveitis is very common in domestic species, primarily dogs, cats, and horses. Causes range from systemic infections (eg, tick-borne diseases, leptospirosis) to immune-mediated disease. Nearly identical uveitis syndromes are observed in humans and dogs, such as Vogt-Koyanagi-Harada disease in humans with its canine counterpart, uveodermatologic syndrome. Similarly, horses develop chronic recurrent uveitis that clinically is very similar to chronic relapsing uveitis in humans. The development of drug implants (cyclosporine, fluocinolone, or dexamethasone) for the long-term treatment of equine and human uveitis was developed simultaneously, and these implants are now some of the most common treatments for these diseases. A unique topical suppressor of cytokine signaling inhibitor for treatment of equine uveitis is also being investigated and, if successful in horses, may have excellent efficacy in treatment of both equine and human uveitis. Immunosuppressive gene therapies are in the preclinical evaluation stages and, if determined safe, may be effective therapies for uveitis in both horses and humans. If approved by the USDA, a clinical trial in horses of the use of an AAV delivering equine IL-10 will be the first of its kind in any animal for the long-term treatment of naturally occurring uveitis. These studies are reviewed in more detail in the companion Currents in One Health by Gilger, AJVR, December 2022.

**Glaucoma**

Glaucoma is associated with an elevated intraocular pressure that leads to vision loss by primarily damaging the retinal ganglion cells and optic nerve. Glaucoma is classified as primary or secondary to other ocular diseases such as uveitis. Primary glaucoma can be further divided into primary open-angle, primary closed-angle, and primary congenital glaucoma.

Although several domestic animals develop glaucoma, it is very common in dogs. In fact, in some dog breeds such as the American Cocker Spaniel, it is particularly prevalent. Although there are some anatomical differences in drainage outflow in the canine eye compared with the human eye (such as no Schlemm’s canal in dogs), there are many similarities between the disease entities of primary canine and human glaucoma. Furthermore, many of the glaucoma treatments used in human medicine are effective in the dog, such as the use of topical prostaglandin analogs. Therefore, shared development of medications, glaucoma surgical procedures, and intracameral implants are mutually beneficial for canine and human patients. Human glaucomas are genetically heterogeneous, and multiple genetic loci have been identified. Recently, genetic associations with canine glaucoma have been determined, including those affecting ADAMTS10, ADAMTS17, myocilin, nebulin, COL1A2, RAB22A, and SRBD1. However, except for myocilin, there is very limited crossover in genetic biomarkers identified between human and canine glaucoma. This lack of known genetic similarities has not stopped the use of the canine glaucoma model to evaluate the efficacy and safety of antiglaucoma medication and devices, such as intraocular implants delivering prostaglandin analogs. Although these sustained-release intracameral implants (Figure 6) are not yet marketed for canine glaucoma, the safety and efficacy of intracameral implants in dogs have been demonstrated and may mark a substantial advance in the treatment of canine primary glaucoma.

**Cataracts**

Cataracts, or opacities of the lens of the eye, develop in most domestic species and can be a result of genetic defects or secondary to inflammation, trauma, or diabetes mellitus (Figure 7). Spontaneous, genetic, and diabetic cataracts are particularly common in dogs. The genetic basis of canine cataracts is being discovered; for example, juvenile cataracts in Wirehaired Pointing Griffon Dogs were shown to be associated with an FYCO1 frameshift deletion. Cataract surgery and intraocular lens placement are common surgeries performed by veterinary ophthalmologists. Surgical technique, instrumentation, and perioperative therapeutics are similar between human and canine patients. One particular area of one health–type research has been...
in the evaluation and prevention of posterior capsular opacity (PCO), a condition that results in development of opacity in the eye and decreased vision from lens epithelial regrowth and/or posterior lens capsule fibrosis after cataract surgery. Dogs develop a rapid and severe PCO after canine cataract surgery. Therefore, dogs (and their lens capsules) have been instrumental in the research of surgical technique, intraocular lens design, drug delivery, and postoperative therapeutics, such as the use of NSAIDS, to prevent the development of PCO in dogs and humans.

Retinal Disease

Study of inherited retinal disease in domestic animals has epitomized the one health concept, specifically the collaborative efforts of multiple disciplines working to attain optimal retinal health for people and animals. Study of inherited retinal degenerations, their genetic basis, and optimized therapies, such as gene therapy in dogs, has revolutionized treatment for these blinding conditions in humans. Work by Drs. Gus Aguirre and Greg Acland in the Briard dog with RPE65 deficient retinal degeneration, a naturally occurring model of Leber congenital amaurosis, paved the way for the development of the first gene therapy approved by the FDA (Luxturna) for treatment of retinal degeneration. Studies of genetic retinal disease in dogs that have human analogues are ongoing, and at least 16 different genetic mutations resulting in retinal degeneration in dogs have been identified (Figure 8). Through this work, innovative therapies to prevent retinal degeneration are being developed.

Conclusions

The study of the etiopathogenesis, pathophysiology, genetics, and treatment of naturally occurring ocular disease in veterinary patients, especially dogs, cats, and horses, translates well to human eye disease because of similarities of ocular anatomy, physiology, and shared environments between animals and humans. These similarities support the collaborative, multisectoral, and transdisciplinary approach that defines the one health initiative. Veterinarians at all levels, therefore, are at the forefront of the one health process through their study of ocular disease, whether it is in their practice, clinic, university hospital, or research laboratory. We all share the one health goal of achieving optimal ocular health for all by recognizing the interconnection between people, animals, and their shared environment.

Acknowledgments

No external funding was used in the development of this manuscript.
The author is listed on a patent owned by the University of North Carolina and North Carolina State University for the treatment of ocular disease associated with mucopolysaccharidosis VI. The author is also listed on a patent owned by the University of North Carolina and North Carolina State University for adeno-associated virus egl10 treatment of equine uveitis. The author also has a financial interest in RainBio Inc, which is commercializing treatment for ocular disease associated with mucopolysaccharidosis I.

References

17. Large TP, Mack S, Villiers E, Oliver J. In vitro susceptibility of canine corneal bacterial pathogens to three cross-linking protocols. Vet Ophthalmol. Published online June 17, 2022. doi:10.1111/vop.13006


