OCULAR MANIFESTATIONS OF SYSTEMIC DISEASE

By Terri Baldwin, DVM, MS
Diplomate ACVO

CANINE

METABOLIC DISEASES

**Diabetes Mellitus** is most commonly manifested as fast developing cataracts. This type of cataract is the result of increased glucose in the aqueous humor. The cataract often has a prominent Y suture line on the anterior portion of the lens, making it the “Yes” for diabetes. Blood glucose is recommended for diagnosis. In fact 85% of all diabetic dogs will develop cataracts within 18 months of diagnosis. New medications are being developed for prevention of cataract formation and are still in the trial phase. Right now the only treatment is surgical removal.

**Hypothyroidism** can cause KCS development in 20% of dogs. In addition, lipid deposits can develop in the cornea. Most commonly these lipid deposits occur at the periphery of the cornea, near the limbus. Therefore testing for hypothyroidism should be performed if there are other concurrent symptoms. Treatment of the hypothyroidism can help reverse these deposits.

**Cushing’s** disease has been associated with KCS, non-healing corneal ulceration, corneal calcification, cataract development, lipid aqueous, and lesions associated with hypertension. In senile dogs, a syndrome of corneal calcification with exfoliation of calcium leading to progressive ulceration is seen most commonly in dogs with Cushing’s disease. Treating the Cushing’s disease can speed corneal healing.

CARDIOVASCULAR DISEASES

**Hypertension** can be defined as systolic BP greater than 160mmHg. Hypertension is associated with renal disease, Cushing’s disease, pheochromocytoma, primary aldosteronism, hypothyroidism, and hyperthyroidism. Initial response to hypertension is constriction of retinal arterioles and with sustained high BP, occlusion and ischemic necrosis occurs of the blood vessel walls. This results in increased vascular permeability. Serous retinal exudates, hemorrhages, and edema occur due to the vascular permeability. In addition, tortuous retinal vessels and hyphema and vitreal hemorrhage can be seen. A blood pressure should be performed anytime there is bleeding in the eye. If the blood pressure can be controlled, then often retinal detachment and hemorrhage can be reversible and vision restored. Some permanent damage is likely.

HEMATOLOGIC DISEASES

Profound **anemia** can cause pale retinal vasculature and varying degrees of retinal hemorrhage. Retinal hemorrhage is worse when there is a concurrent thrombocytopenia. The cause of the hemorrhage is hypoxia of the vessel walls. Hemorrhage usually resolves once the anemia is treated.
**Hyperlipidemia** has been associated with hypothyroidism, diabetes, Cushing’s disease, and pancreatitis. Also various breeds (Schnauzer, Beagle, Briard, Collie, and Sheltie) have been known to have primary hyperlipidemia/hypercholesterolemia. It has been associated with lipemic aqueous, which appears as if milk has been poured into the anterior chamber, and peripheral lipid deposits in the cornea near the limbus.

Lipemic aqueous can be associated with a previous fatty meal and can have a concurrent corneal ulcer. The ulcer can cause a reflex anterior uveitis, which leads to increased permeability of the vessels in the anterior segment, resulting in diffusion of lipid into the aqueous. Treatment of the inflammation usually leads to rapid absorption of the lipid. A quick method of diagnosis is to draw a blood sample and spin it down. The serum will be heavily lipid laden. Further evaluation would include fasting blood work to look for elevated lipid, cholesterol, T4, and/or triglycerides. Questran orally (1 teaspoon – 1 tablespoon 2 times daily in the food) can reduce the deposition in the aqueous humor and is often used in lipemic dogs after cataract surgery.

**Hyperviscosity Syndrome** is seen when the total blood protein is very elevated. In dogs, this is most commonly associated with hyperglobulinemia from either chronic inflammatory diseases (e.g. tick borne) or from multiple myeloma. This can cause severe retinal vascular tortuosity, retinal hemorrhage, retinal edema and/or detachment, and diffuse intraocular hemorrhage. Secondary glaucoma can be seen as well. Complete bloodwork plus tick panel and/or protein electrophoresis can determine the underlying cause. Treatment is aimed at controlling the underlying disease and there can be improvement in the intraocular disease.

**Thrombocytopenia and thrombocytopathies** can cause varying degrees of intraocular hemorrhage. Thrombocytopenia usually causes more petechial type of hemorrhaging and is seen most often in retina and subconjunctival space. This is seen most commonly with ITP and arthropod-borne disease (Babesia, Borrelia, Cytaxxoon, Dirofilaria, Ehrlichia, Leismania, and Rickettsia). In general platelet counts usually have to be lower than 50,000 in order to cause ocular hemorrhage. Diffuse intraocular hemorrhage or large areas of subconjunctival hemorrhage is often due to clotting disorders such as with von Willebrand’s, DIC, liver failure, and rodenticide toxicity. Therapy is directed at treating the underlying disorder.

**INFECTION ous DISEASES**

**Bacterial**

*E. coli* infection from pyometra can result in anterior uveitis and chorioretinal hemorrhages or exudates. Diagnosis is by culture or concurrent other illness. *Bartonella, Borrelia (Lyme), Rickettsia (RMSF), and Ehrlichia* infections can occur from tick transmission. They can cause anterior and posterior uveitis, hemorrhage, and retinal detachment. Diagnosis is by serology. Treatment for these diseases is appropriate antibiotics and anti-inflammatory therapy.

*Brucella* also causes chronic uveitis and hyphema and has been reported to be seen in 14% of all cases. *Leptospira* is becoming an increasingly more common cause of uveitis in the Midwest. It is most commonly seen in pets from the suburbs that come into contact with wildlife, especially Raccoons. Both *Brucella* and *Leptospira* are zoonotic
and can develop carrier or chronic states. Serological testing is required for definitive diagnosis.

Fungal

**Blastomycosis** is most common cause of ocular fungal infection in the Midwest. Most cases live within 90 meters of water. Clinical signs depend on organ system it is affecting. Ocular involvement occurs in nearly 50% of all cases. Ocular symptoms are of a quick development of panuveitis with posterior uvea most severely affected. One or both eyes may be affected. Usual presentation is acute pain, redness, cloudy cornea, and loss of vision. It affects the ventral non-tapetal area of the retina first and then will cause complete retinal detachment and often secondary severe glaucoma. Titers are unreliable, but the Urine Antigen test from MiraVista is more accurate. Prior to this test, finding the organism was the only reliable way to diagnose the condition. Particularly sensitive is subretinal aspiration of the exudates, which is reported to be nearly 100% sensitive. This procedure is performed in blind eyes to reduce pressure and diagnose the disease.

Another common infection in the Midwest is *Histoplasmosis*. Ocular lesions occurred in 66% of dogs and occurred most commonly in the anterior choroid, iris, ciliary body, and sclera. The choroidal infection leads to subretinal granulomas and focal retinal detachment, which is generally much less severe than Blastomycosis. Optic neuritis and anterior uveitis can also occur. Serologic testing is more accurate than with Blastomycosis, but a negative test does not rule out the disease.

Other less common fungal infections include *Cryptococcosis* and *Coccidiomycosis* and *Aspergillosis*. Cryptococcosis and Aspergillosis cause predominantly posterior uveitis with choroidal infection and retinal detachment, whereas Coccidiomycosis causes predominantly anterior uveitis. Cryptococcosis and Coccidiomycosis can be diagnosed more reliably on serology, where Aspergillosis is best diagnosed by demonstrating the organism.

Treatment of the fungal diseases relies on using the appropriate anti-fungal therapy after diagnosis. Generally long term therapy of greater than or equal to 6 months results in more cures than short-term therapy of 3 months. There is a controversy on whether to use systemic steroids in addition to the anti-fungal therapy. Most internists and ophthalmologists agree that an anti-inflammatory dose is safe when given concurrently with the appropriate anti-fungal therapy. This helps to reduce the likelihood of completely retinal detachment in dogs with focal lesions. When the CNS is involved, the prognosis for recovery is grave.

Viral

**Canine Distemper Virus** is caused by Morbillivirus in the Paramyxoviridae family and is spread by inhalation of viral particles. Acute ocular signs include bilateral conjunctivitis with serous ocular discharge that progresses to mucopurulent discharge. KCS can develop secondary to lacrimal adenitis development. It often produces a multifocal non-granulomatous chorioretinitis. These lesions progress to hyperreflective scars that are often called bullet lesions. Rarely do the chorioretinal lesions lead to diffuse retinal degeneration. The worst ocular symptom is acute blindness due to bilateral optic
neuritis. Diagnosis can be made from fluorescent antibody stains on conjunctival scrapings. KCS is treated with topical antibiotics and tear stimulants and optic neuritis is treated with steroids. The prognosis for dogs with neurologic disease (ie optic neuritis) is very poor.

PARASITIC

Toxoplasmal, Neosporal, Leishmanial, and Hepatozoonal infections can also affect the eyes. With Leismania and Hepatozoon, the ocular clinical symptoms are usually consistent with conjunctivitis, KCS, and anterior uveitis, whereas the posterior segment is usually spared. Toxoplasma and Neospora infections usually have symptoms of retinitis with choroidal extension, anterior uveitis, and extraocular myositis. Neospora is more common in dogs than Toxoplasma and is usually most commonly characterized as an ascending paralysis with hindlimb hyperextension. Toxoplasma usually only occurs in immunocompromised dogs. Diagnosis is usually based upon serology or finding the organism.

NEOPLASIA

Lymphosarcoma is the most common secondary intraocular neoplasia of the eye in dogs and usually affects both eyes. It is may even be the only presenting complaint. The anterior uvea is more greatly affected, but retinal hemorrhage and posterior uveitis may also be seen. The irides are usually very thickened and hypopyon may be present in the anterior chamber. When the eye is affected, the lymphoma is considered a stage V, so often peripheral lymphadenopathy is present as well. Diagnosis can be made by aspiration of the anterior chamber or by aspiration of peripheral lymph nodes. When the eye is involved, the prognosis for survival is lower. Secondary glaucoma is a common complication to lymphoma due to blocking of the drainage angle. Topical steroids and anti-glaucoma medications are very important in reducing the inflammation and pressure quickly so that vision can be saved. Systemic chemotherapy is also critical.

Other tumors can metastasize to the eye. Diffuse intraocular hemorrhage can be caused by metastasis of hemangiosarcoma. Other reported tumors to metastasize to the eye include melanoma; adenocarcinoma of the pancreas, mammary, salivary, sweat gland, and thyroid; squamous cell carcinoma, transitional carcinoma, mast cell tumor, and TVT. Treatment is usually limited because these usually occur late in the course of these tumors.

IMMUNE-MEDIATED

Uveodermatologic Syndrome, or VKH, is most commonly seen in Artic Circle breeds of dogs. With this disease, there is an auto-immune attack on melanocytic cells resulting in depigmentation of the face and hair with it most commonly affecting the eyelids, nasal planum, and lips. Ocular lesions vary from anterior uveitis to severe panuveitis with retinal detachment and loss of vision. Secondary glaucoma and cataracts are common. Treatment includes use of topical and systemic steroids, often in conjunction with Azathioprine, Atopica, or Cyclophosphamide. Prognosis is poor.
KCS is most commonly caused by an autoimmune attack on the lacrimal glands. This causes dysfunction and resultant decrease in the aqueous portion of the tears. Treatment with T-cell suppressors, such as Tacrolimus and Cyclosporine can result in control of the disease. In 85% of dogs with atopy, KCS was diagnosed concurrently. In addition, this disease is more often to be exacerbated during more active allergy seasons.

FELINE

METABOLIC

Diabetes rarely causes cataracts in cats unless they are diagnosed under the age of 4 due to the types of enzymes they have in their lens that metabolizes the glucose. However, diabetic retinopathy is more likely to occur in cats than dogs due to the longer lifespan after diagnosis. This is exhibited as retinal hemorrhage and detachment, with microaneurysms also being detected.

Hyperthyroidism can cause retinal arterial tortuosity. Since hyperthyroidism can cause hypertension as well, retinal detachment and hemorrhage can be seen as well. In general prompt treatment of these conditions, can lead to retinal reattachment and recovery of vision.

CARDIOVASCULAR DISEASES

Hypertension is one of the most common causes of retinal detachment in older cats. It is often associated with chronic renal insufficiency, hyperthyroidism, and hypertrophic cardiomyopathy. Ocular symptoms include serous bullous retinal detachment with intra- and pre- retinal hemorrhages, vitreal hemorrhage, and hyphema. Most cats have very elevated BPs of well over 200mmHg. In the majority of cases, lowering the BP will result in retinal reattachment and recovery of vision, especially if the retina is reattached within 1 month. Complications can occur leading to permanent vision loss and usually include retinal tearing with disinsertion or secondary glaucoma. Amlodipine is considered the treatment of choice.

HEMATOLOGIC DISEASES

Anemia can also cause retinal hemorrhages in cats, as well as dogs. The most common cause of the severe anemia is Mycoplasma haemofelis (previously Hemobartonella). Symptoms usually resolve with correction of the anemia.

Thrombocytopenia or Thrombocytopathy can cause petechia in the fundus often without visible petechiae in the skin or mucous membranes. The most common causes of thrombocytopenia include infection with Babesia, Cytauxzoon, and Ehrlichia; FIV, panleukopenia; histoplasmosis; neoplasia (lymphoma, multiple myeloma, leukemia).

Hyperviscosity Syndrome is seen when the protein content in the blood stream is very high. This is most commonly seen in cats with neoplasia such as multiple myeloma, lymphoma, leukemia, or plasmacytoma but can also be seen with FIP. Ocular symptoms
include retinal hemorrhage and detachment, as well as hyphema. Diagnosis can be
determined usually by performing bloodwork and protein electrophoresis.

**INFECTION DISEASES**

**Bacterial**

*Bartonella* infections have been recently demonstrated to be a common cause of
anterior uveitis. Other symptoms include blepharitis, conjunctivitis, keratitis, and
chorioretinitis. These infections are usually transmitted from fleas and are responsive to
Azithromycin. Diagnosis is based upon positive serology.

*Chlamydophila (Chlamydia)* infections are a common cause of acute and
chronic conjunctivitis. The conjunctivitis may start out in 1 eye but then progresses to the
other eye in a few days. Diagnosis can be made with ELISA antigen or PCR tests, or
demonstrating the organism on cytology. The conjunctivitis usually resolves with
treatment with either Erythromycin (less irritating) or Terramycin 2-3 times daily for 2-3
weeks. In chronic cases, systemic treatment with Azithromycin or Doxycycline has been
successful.

**Fungal**

*Cryptococcus* is the most commonly reported feline fungal disease. It can cause
chorioretinitis with granulomatous inflammation and retinal detachment. Anterior
uveitis and optic neuritis can also occur. *Blastomycosis* can cause chorioretinitis in cats
as well although it is not as common as in dogs. *Histoplasmosis* and *Coccidioidomycosis*
can cause similar lesions in cats as well. Demonstrating the organism on cytology or
histopathology samples results in a diagnosis. Treatment involves topical therapy with
anti-inflammatory medication and Itraconazole appears to be most effective for anti-
fungal therapy.

*Dermatophytosis* causes periocular alopecia and eyelid ulceration. Diagnosis is
made with use of DTM. Treatment for this disease involves clipping the periocular hair
and applying miconazole or enilconazole or systemic treatment of itraconazole or
griseofulvin.

**Viral**

*Herpesvirus* is the most common cause of ocular disease in cats. Population
studies indicate that the disease has 95% prevalence and of this population, 80% of cats
develop a latent infection in the trigeminal nerve that supplies the eye. Approximately
45% of these cats shed the virus throughout their lifetime. The disease is most commonly
transmitted from ocular or nasal secretions in cats actively shedding the disease. It is
most commonly seen unilaterally but can be seen bilaterally.

The disease most commonly causes conjunctivitis and keratitis in cats, but has
also been implicated as a possible cause of anterior uveitis. Dendritic corneal ulcers are
pathognomonic for the disease but punctate and geographic ulcers are also commonly
seen. It develops after reactivation of the virus and this is most commonly due to stress,
illness, or use of steroids. In fact, many cats on chronic steroids for IBD or stomatitis or on chemotherapy for Lymphoma develop Herpes ocular infections.

Common complications of the disease include symblepharon where the conjunctiva and cornea are both ulcerated and adhere together; corneal sequestrum due to chronic geographic ulceration; and eosinophilic keratitis. Symblepharon is often permanent and surgical correction seems to be only temporary as the adhesions recur. Corneal sequestrum most commonly requires superficial keratectomy, but can be recurrent. Eosinophilic keratitis is due to an immune response to the herpes virus infection and is one of the only times topical steroid use is recommended in cats.

Treatment of herpesvirus keratoconjunctivitis depends on the severity. Mild conjunctivitis cases are often self-limiting and don’t require therapy. More severe conjunctivitis and keratitis are best treated with topical anti-virals and antibiotics if ulcerations are present. In geographic corneal ulceration, debridement of the cornea is often necessary to speed healing. Under no circumstances should a grid keratotomy be performed due to its association with the development of corneal sequestrums.

Topical antivirals that are most commonly used include Idoxuridine, Cidofovir, and Vidarabine. The antivirals only kill the virus when it is outside of the cells, therefore frequent administration (TID-QID) is often necessary. In addition, topical interferon has been anecdotally reported to be beneficial.

Oral medications to aid in treatment include Lysine at 500mg PO BID in adults and 250mg BID in kittens. This amino acid reduces the uptake of Arginine, which the virus needs in order to make more viral particles. It is often good for adjunctive therapy or preventative therapy but usually does not control the infection alone. Famciclovir has shown lots of promise in treating resistant infections. This drug has been reported to be much more safe than previous oral antivirals, but a few reports of non-regenerative anemia have been seen. Recommended doses vary considerably as research suggests the best dose to be 90mg/kg PO BID for 1 week, then 90mg/kg SID for 2 weeks. However, ophthalmologists have seen good success at lower doses (30mg/kg BID for 1 week, then 30mg/kg SID for 2 weeks), which may end up being safer in cats. Pre- and post-medical therapy bloodwork is recommended to watch for non-regenerative anemia.

Other common viruses that can cause ocular disease include FeLV, FIV, and FIP. These diseases most commonly cause anterior and/or posterior uveitis. FeLV is most commonly associated with causing lymphosarcoma, which can cause uveitis. FIV can cause a par planitis with white anterior vitreal debris being most commonly seen. FIV appears to often be associated with Toxoplasmosis. FIP causes a bilateral granulomatous uveitis with thick mutton fat keratic precipitates

PARASITIC

Toxoplasmosis is a protozoal infection that is a common cause of ocular disease in cats. Ocular disease is most often associated with systemic disease such as anorexia, fever, hepatitis, myositis, pneumonia, diarrhea, and neurological dysfunction. Ocular disease includes anterior and/or posterior uveitis. Focal bullous retinal detachments are possible as well. Cats with active ocular disease often have concurrent FIV infection. Diagnosis is made by serology and treatment includes topical and oral steroids and oral Clindamycin. Uveitis may become chronic or recurring.
NEOPLASIA

**Lymphosarcoma** is the most common cause of metastatic neoplasia to the eye in the cat. Symptoms include profound iridal thickening with uveitis and hypopyon is commonly present in the anterior chamber. Chorioretinitis with retinal detachment is also seen, causing loss of vision. Glaucoma is a common complication of the uveitis. Ocular disease can commonly precede other clinical symptoms associated with the cancer. Diagnosis is made on cytology. Aggressive therapy with topical steroids and systemic chemotherapy is necessary. Secondary glaucoma may need to be treated as well.

Metastasis of carcinomas is also seen regularly in cats. The most common tumors reported include **Mammary Gland Adenocarcinoma**, **Uterine Adenocarcinoma**, and **Pulmonary Carcinoma**. **Multiple Myeloma** causes secondary ocular disease due to the hyperviscosity syndrome.

NUTRITIONAL

**Taurine Deficiency** is the most common nutritional deficiency to cause ocular disease. Taurine is essential for photoreceptor survival. Deficiency of taurine causes retinal degeneration that begins as a granular appearance to the area centralis, which then develops into a hyperreflective focus, and then can progress to a horizontal streak, and then to an overall diffuse retinal degeneration. This can cause loss of vision. Since most commercial foods contain adequate taurine, this disease is most commonly seen in cats fed inappropriate diets or those with intestinal disease resulting in altered protein absorption.