Ocular Manifestations of Systemic Disease

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A thorough ocular examination should be a part of every physical exam but in patients who are systemically ill, the eye exam can be particularly valuable for uncovering the underlying disease process. The following notes will highlight some of the more common systemic diseases that lead to lesions in the eye. In many cases, the appearance of a lesion can help narrow a differential list and give indications for treatment plans and prognosis.

Diabetes Mellitus
Diabetic cataracts are the most common ocular complication of diabetes in the canine patients. 75% of canine diabetics will develop cataracts within 2 years of diabetes diagnosis. Corneal endothelial changes leading to corneal edema, KCS, and diabetic retinopathy (microaneurysms) are also associated with diabetes. Diabetic cataracts are uncommon in cats as felines have lower levels of aldose reductase. Cataract formation occurs when the primary glycolytic pathway's enzyme, hexokinase, is exhausted and excess glucose is shunted to the sorbitol pathway. The aldose reductase forms sorbitol inside the lens. Sorbitol is a large molecule that does not readily diffuse through cells membranes so an osmotic gradient is created that draws water into the lens fibers, causing them to burst.

The damaged lens fibers (which appear as cataract opacities) start in the peripheral equator of the lens. When examining the lenses of diabetic patients, it is important to dilate the pupils to evaluate for changes in the periphery. If cataracts are detected, it is recommended that the patient be placed on prophylactic, non-steroidal drops (i.e. diclofenac, flurbiprofen or ketorolac 1 drop BID) to avoid complications of lens-induced uveitis. The rapid osmotic swelling of the lens can lead to a sudden rupture of the lens capsule with resultant devastating inflammation. These eye should be treated with aggressive anti-inflammatory medications (topical steroids (Dexamethasone or Prednisolone acetate 1 drop QID) and NSAIDs (Flurbiprofen, Diclofenac, Ketorolac 1 drop BID), topical atropine (1 drop BID) and oral NSAIDs and taken to surgery as soon as diabetic regulation will permit. The ideal timing for diabetic cataract surgery is as soon as the cataract impairs vision but *prior to a sudden lens capsule rupture.* Once the lens capsule rupture occurs, complications such as secondary glaucoma and persistent inflammation are more common.

Juvenile Pyoderma/Cellulitis (Puppy Strangles)
Juvenile cellulitis typically affects puppies younger than 8 months and manifests as pustules on the periocular skin, pinna and muzzle. Regional lymphadenopathy is often dramatic. While the granulomatous lesions are typically sterile, there can be a secondary bacterial component so the recommended treatment is immunosuppressive doses of oral steroids with a systemic broad-spectrum antibiotic for 3 weeks beyond the resolution of clinical signs. Gentle cleansing and a topical antibiotic/ steroid eye drop can also be used.

Coagulopathy
There are many intraocular causes for blood inside the eye from trauma to retinal detachment to invasive tumors. However, when a patient presents with blood inside the eye (hyphema in the anterior chamber,

blood in the vitreous, or retinal petechia), a systemic coagulopathy should be considered. Typical workup should include CBC with platelet count, chemistry with attention to liver enzymes and function, coagulation panel including PT/ PTT, and blood pressure measurement (especially if a retinal detachment is suspected). Infectious titers should include tick-borne disease (*Ehrlichia* spp, *Rickettsia* spp), fungal (*Histoplasma*) and bacteria (*Leptospira* spp.).
Petechia in the retina can often be seen prior to evidence of bleeding elsewhere in the skin or mucous membranes. The presence of blood in the retina is often indicative of a platelet count less than 50,000cells/ul. Therapy should be directed at the underlying cause of the coagulopathy with transfusions administered as needed.

Sudden Blindness

Causes for blindness vary significantly and uncovering the cause depends on determining which structure of the eye or nervous system is the source of the problem. A sudden cataract can be detected with an examination and high intraocular pressure can be verified with tonometry, but changes to the retina, optic nerve or brain can be more difficult to verify.

Common Causes of sudden blindness related to the retina or central nervous system:

1. Toxicity: Enrofloxacin-retinopathy in the cat and Ivermectin toxicity in the dog are common causes of vision loss. In both scenarios, patients will present with vision loss and dilated pupils.
The reported clinical history is often the best evidence of toxicity in these cases.
Enrofloxacin-associated Retinal Toxicity has been shown to cause a sudden and often complete toxic effect on the retina leading to acute blindness. While this is generally associated with doses higher than the manufacturer's recommend dose of 2.5 mg/kg PO every 12 hours, other factors can increase the risk of toxicity including old age, renal or hepatic impairment, and IV route of administration rather than oral. Cat receiving enrofloxacin should be monitored closely for pupil dilation, decrease in vision or grey changes to the retina. Should any of these signs appear, enrofloxacin administration should be stopped immediately. When possible, alternative antibiotics should be chosen.

2. Immune-mediated disease: Uveodermatologic disease (VKH-like disease) describes an immune-mediated destruction of melanocytes in the eye and the skin. Bilateral uveitis and retinal detachments are common and lifelong immunosuppressive medications are necessary. Granulomatous Meningoencephalitis (GME) is another immune-mediated attack that leads to blindness through inflammation around blood vessels and nervous tissues including the optic nerve. Swelling of the optic nerve can respond to steroids but the long-term prognosis is guarded.

3. Retinopathy: If a patient presents with sudden blindness and dilated pupils in the absence of any signs of ocular inflammation, a retinal lesion should be suspected. Retinal exam may reveal a decrease in retinal vessel size or tapetal hyperreflectivity consistent with age-related degeneration or breed-related Progressive Retinal Atrophy. Alternatively, Sudden Acquired Retinal Degeneration syndrome (SARDs) can present with a retina that is normal in appearance. The electroretinogram (ERG) is the key diagnostic tool to determine whether the retina is functioning normally. While there is no reliable treatment to restore vision in retinal degeneration, owners are often relieved to verify (via ERG) that the retina is the source of the blindness rather than a central nervous system lesion. An ERG in the awake patient helps owners avoid the cost and anesthesia required for MRI.

4. Neoplasia: A thorough cranial nerve examination that demonstrates absent menace response with normal pupil size and PLRs is suggestive of a lesion in the occipital cortex (visual cortex) as the retinas are capable of transmitting information to the brainstem as evidenced by the PLRs. While CNS infection and vascular lesions also occur, neoplasia is the most common explanation and a recommendation of MRI and CSF tap offers the best chance for a diagnosis or treatment options.

5. Systemic Hypertension: High blood pressure leading to bilateral retinal detachment can be confirmed with a blood pressure reading and treatment should be initiated immediately. MAP readings greater than 200mmHg suggest that blood pressure can be the cause of a sudden and blinding retinal detachment. Systemic hypertension is commonly associated with advanced age, chronic renal failure and hyperthyroidism in cats.

While it is important to determine the underlying cause, treatment with Amlodipine (starting dose of 0.625mg PO SID in most cats) should be initiated as soon as possible and blood pressure rechecked in 3-5 days to increase medication to BID as needed. Additional medications may be required. Control of the blood pressure within the first two weeks of presentation will provide the greatest chance for retinal reattachment and vision return. Unless there is an associated uveitis caused by a retinal vessel bleed, topical ocular medications are generally not needed.

Infection, immune-mediated, and neoplastic causes of Uveitis from systemic disease

Uveitis describes inflammation of the uveal tract of the eye (iris, ciliary body and choroid) as when patients present with bilateral inflammation, the index of suspicion for systemic disease should be high. Animals with uveitis can show a number of different signs, including pain, aqueous flare (prostaglandins, fibrin and white blood cells), miosis, conjunctivitis, corneal edema, or low intraocular pressures. In many cases, the debris (aqueous flare) clogs the iridocorneal angle, leading to high pressures and vision loss associated with secondary glaucoma.

Many different conditions can cause uveitis in dogs and cats. In general, they can be categorized into four large groups: infection, neoplasia (cancer), trauma, and immune-mediated. Infection would include bacterial, viral, and fungal infections (including Rocky Mountain Spotted Fever, Ehrlichia, Feline Leukemia Virus, Bartonella, Toxoplasmosis and fungal diseases with ocular manifestations such as Blastomycosis, Cryptococcosis, Histoplasmosis and Aspergillosis). Neoplastic possibilities include lymphosarcoma (37% of LSA cases have ocular signs), multiple myeloma, and metastatic lesions. Trauma would include blunt trauma (blow to the head), and penetrating trauma (cat scratch to the eye). Immune-mediated examples include uveodermatologic disease (VKH-like) or phacoclastic (lens-induced) uveitis in which the body reacts to leaking lens material with a traumatic or diabetic cataract. In all cases of uveitis, it is important to try to determine the underlying cause with bloodwork and radiographic studies, so that it may be appropriately treated. Unfortunately, in up to 75% of uveitis cases the cause is never determined.

Treatment of Uveitis:
Uveitis must be treated aggressively in order to prevent permanent damage to the eye. The inflammation causes white blood cells and fibrin to accumulate in the anterior chamber. This debris clogged the drainage angle and can lead to secondary glaucoma. Even after the uveitis has resolved, the glaucoma may persist if the drainage structures were permanently damaged. Different medications are used to control the underlying cause of the uveitis and to minimize the inflammation itself. Anti-inflammatory medications can be given orally and in the form of eye drops. Topical drops (Prednisolone acetate 1% or Neo-Poly-Dexamethasone 0.1% 1 drop 3-4 times daily) should be used. Topical non-steroidals (Diclofenac, Flurbiprofen, or Ketorolac 1 drop 2-3 times daily) can also be used. While topical NSAIDs are less likely to inhibit corneal healing in the face of a corneal ulcer, they should nonetheless be used with caution as they have been implicated in corneal melts. Oral steroids or NSAIDs may also be prescribed at anti-inflammatory doses, particularly if the inflammation involves the structure of behind the iris where topical medications do not effectively penetrate. Topical atropine (1 drop 1-2 times daily) may also be given to alleviate pain by decreasing ciliary spasm of miosis, prevent posterior synechia scarring and stabilize the blood-aqueous barrier that is leaking and creating aqueous flare. Oral and topical antibiotics may be given if the cause of the uveitis is an infection or corneal ulcer.

Prognosis:
Uveitis will usually resolve with no complications if it is caught and treated early. As has been mentioned previously, it is very important to also determine and treat any underlying cause of the uveitis. Many tests may be needed to make this determination, including bloodwork (CBC/ Chemistry/UA/infectious titers), radiographs, and ultrasound. Unfortunately, in some patients the cause of the uveitis is never found, and treatment may be lifelong. In other patients, uveitis is so severe that it may be necessary to remove the eye.