Pepper's Ocular Predicament

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Introduction

Hereditary cataracts are the most common form of cataracts in purebred dogs. [(1)] Breeds with proven or suspected inherited cataracts include Labrador and Golden retrievers, many terrier breeds, American and English cocker spaniels, and many more. [(1)] Development of hereditary cataracts is poorly understood in dogs. Research is still being performed to determine the genes that may be involved in hereditary cataract formation. In this paper we will focus on the Labrador retriever and heritable cataracts.

History and Presentation

Pepper is an approximately 16-month-old, female intact Labrador Retriever. She presented to her DVM during hunting training for missing the decoys and running into things, which she had not done previously. Pepper was seen by her veterinarian on June 8, 2020 for coughing. At this time, she was diagnosed with a cataract in her left eye. Pepper was then seen on June 12, 2020 at her veterinarian and she was diagnosed with a mature cataract in the left eye and an immature cataract in the right eye. Pepper presented to MSU CVM Ophthalmology service for evaluation of her cataracts on June 16, 2020.

On presentation, Pepper was bright, alert, responsive. At this time a weight was not obtained due to concern that she was just recovering from kennel cough. She was a body condition score of 4/9. Her heart rate was 90 beats per minute. Respiration rate was 36 breaths per minute. The only abnormality present on physical exam was bilateral cataracts with the cataract in the left eye being more progressed than the one in the right eye.

Pathophysiology

The lens has three main components: the lens fibers, capsule, and anterior epithelium. [1] The lens is divided into two general parts: the cortex and nucleus. The nucleus is the central region with the cortex being the outer region of the lens. The lens consists of anterior and posterior surfaces, with the centers of these surfaces being the anterior and posterior poles, respectively. The circumference of the lens is known as the equator. The lens itself is composed of lens fibers. These fibers are produced throughout life. The fibers are produced in the area of the cortex, build onto the existing fibers, and force the older fibers into the center or nucleus.

The lens is suspended by zonular fibers (lens zonules). These fibers attach at the equator of the lens on one end and the ciliary body on the other. The lens is suspended behind the iris and the pupil. Lens zonules change the refractive power of the lens through the tension that is placed on them by the ciliary body muscle. This ability of the lens allows it to focus light on the retina. Another capability of the lens is to filter out UV light, specifically UV-B radiation, which protects the retina from the effects of ultraviolet radiation. [1]

The lens is avascular and receives its nutrients through the aqueous humor. The aqueous humor provides glucose to the lens, which is broken down to lactic acid anaerobically through the hexokinase pathway. If there is a disruption in the composition of the aqueous, then that affects the transparency and metabolism of the lens. Transparency in the lens in sustained through a number of intricate factors. [2] The lens fibers have a low cytoplasmic density due to a decreased number of cell nuclei and intracellular organelles. Lens fibers have a complex matrix arrangement that assists with transparency of the lens.

In general, anything that effects lens or protein metabolism, nutrition, or osmotic balance of the lens causes opacification of the lens. [1] The lens is composed primarily of soluble proteins with a minor amount of insoluble proteins. Increase in the amount of insoluble proteins leads to

increased opacification of the lens. There is also an increase in the amount of proteolytic activity within the lens that results in degradation of the cell membranes as well as the lens proteins. [1] Decrease in Na-K+ ATPase pumps in the lens epithelium results in an ionic shift that is detrimental to the lens. [2] There is also a decrease in oxygen consumption and ATP production. Antioxidant activity within the lens is decreased, such as decrease in Vitamins E and C, increase oxidized or reduced glutathione levels, and decrease in superoxide dismutase. [2] Ionic concentration, hydration of the lens, and other metabolic functions specific to the lens can further affect the lens opacity. [2]

There are multiple ways that cataracts can be classified including: cause, age of onset location or stage of progression. [2] Stage of cataract development is the most clinically relevant and widely used classification system. [1,2] In this classification scheme there are four groups: incipient, immature, mature and hypermature. Incipient cataracts are early cataract changes. [2] Incipient cataracts are focal opacities on the lens, with the rest of the lens remaining transparent. [1] Dogs with incipient cataracts are still visual, and they should have no lens induced uveitis (LIU). Surgery is not recommended for incipient cataracts. [1] These cataracts usually involve Y-suture, cortical or subcapsular areas of the lens. [2]

Immature cataracts are the next stage and are more extensive with majority of the lens included. [1] The classic feature of this stage is area of cataracts that are less dense or may have regular lens fibers. [2] The lens has increased opacity but tapetal reflection can still be seen. [1] However, details of the fundus may be obscured during an ophthalmologic exam. Mature cataracts involve the whole lens, animals with this form of cataract are blind. [1,2] There is no tapetal reflection and the fundus cannot be visualized. Lens induced uveitis is likely occurring. [1] Hypermature cataracts are mature cataracts that begin to liquefy due to an increase in proteolysis.

This causes protein and fluid to leak from the lens and results in the characteristic appearance of wrinkling in the area of the cortex. [2] At this stage lens induced uveitis is severe. [1,2]

While the pathophysiology of cataracts has been discussed, the development of heritable cataracts is poorly understood. [1,2] There is an apparent genetic component. A study performed in Labrador retrievers in the Netherlands indicated that there is a genetic component involved in cataract formation. [4] This study also showed that different phenotypes of cataracts formed in families, and therefore concluded that they must all be from the same genetic mutation(s). Another study suggested that GALK1 gene maybe the cause of cataracts in Labrador retrievers. [3] However, they couldn't identify an intron or exon mutation that could be the culprit. They did suggest that something outside of the exon maybe a cause, but it has not been investigated further. In Labrador retrievers there are two forms of cataracts that have been documented most commonly: "posterior subcapsular and progressive cortical cataracts." [2] It appears that these heritable forms of cataracts are transmitted as a dominant trait but have incomplete penetrance. [1,2]

A 2006 study showed that mutations in the HSF4 gene may be the cause of hereditary cataracts in three dog breeds. [6] The authors showed that the mutation in this gene was linked to hereditary cataracts in the Boston terrier, Australian shepherd and Staffordshire Bull terrier. HSF4 is a "heat shock transcription factor." These transcription factors control the production of heat shock proteins during periods of stress. In humans autosomal dominant as well as autosomal recessive cataracts are caused by various mutations in the HSF4 gene.

Differential Diagnoses

Given Pepper's age and obvious cataracts, heritable cataracts were the number one differential in this case. Other causes of cataract formation are systemic disease that results in cataract formation, cataracts that are a result from medications or toxic substances, nutritional deficiencies, traumatic injury to the lens, and inflammation of the lens. [(2)] Things that could be ruled out due to age were age related cataracts and nuclear sclerosis. Pepper had no history of nutritional deficiencies, had no evidence of systemic illness that might lead to cataract formation, no evidence or history of traumatic eye injury or inflammation associated with the eye/lens, and had no history of receiving or getting into medications or toxic substances that could have resulted in cataract formation.

Diagnostic Approach/Considerations

On presentation, a full ophthalmologic exam was performed. Menace response, tracking, and dazzle reflex were all intact. The size position and motility of the globe was also normal in both eyes. Nictitating membrane and conjunctiva were normal in both eyes. A Schirmer tear test was performed in each eye, and the results were normal with 20 mm/min in the right eye and19 mm/min in the left eye. Fluorescein stain was used to stain both eyes to check for evidence of corneal defects. No defects were appreciated in either eye. Intraocular pressure was obtained from both eyes and was normal with 15 mmHg in the right eye and 10 mmHg in the left eye.

Pupils were normal in both eyes, with intact direct and consensual pupillary light reflexes. Slit lamp biomicroscopy showed no cellular material and no flare present in the anterior chamber in both eyes. The right lens had a posterior cortical cataract with vacuoles at the equator. The left lens was completely opaque with no tapetal reflex, consistent with a mature cataract. The eyes were dilated, and indirect ophthalmoscopy was performed. The fundus was unable to be viewed in the left eye, but in the right eye there was a partial view. The vitreous

appeared normal in the right eye. Examination of the fundus showed a normal fundus in the right eye. At this time, she was sent home with ketorolac ophthalmic drops to be placed in both eyes twice a day until she returned for surgery. Ketorolac ophthalmic solution was given as an anti-inflammatory pre-operatively.

Pepper returned to MSU CVM Ophthalmology department on June 29, 2020. At this time, she weighed 24 kg. Her physical exam was like the one previously performed on June 16. At this time, an electroretinogram and ocular ultrasound were performed. Electroretinography measure the electrical potentials that the retina produces when light strikes it. [(1)] Lights of various wavelengths, intensities, and flash frequency are shown to the retina, and the retina's response to these things is measured by electrodes that are placed around the eye of the animal. These responses are then made into a waveform which shows the responsiveness of the retina. [(1)]

Ocular ultrasound is particularly useful for cataractous eyes that are completely opaque by allowing visualization of the structures posterior to the lens. It is also useful for looking at the orbit and surrounding structures. [(1)] Both ERG and ocular ultrasound were within normal limits for Pepper. A complete blood count, serum chemistry panel, and urinalysis were performed since she had a history of fever or unknown origin that was not worked up. Complete blood count showed a mild anemia. Serum chemistry panel showed a mildly elevated creatinine. Urinalysis results showed a urine specific gravity of 1.052 with trace protein.

Given these results, a renal workup including abdominal radiographs and ultrasound was pursued. Abdominal radiographs showed normal kidneys and mild osteoarthritis in the coxofemoral joints. Abdominal ultrasound was normal. Both kidneys had normal margination, echogenicity and shape. Color doppler interrogation was performed over both kidneys and showed normal blood flow. A cause for the renal azotemia could not be determined from the

abdominal ultrasound and radiographs. Therefore, it was decided that the azotemia was due to a pre-renal cause.

Treatment and Management Options

There are two options for treatment of cataracts: medical and surgical. There are no medical therapies that can delay or halt cataract progression. [1,2, 7] There is some evidence that aldose reductase inhibitors maybe useful in dogs with diabetic cataracts. [2] Some things to consider if owners opt for medical management are treatment of lens induced uveitis, regularly checking intraocular pressures, checking tear production and having regular ophthalmic exams performed. [2] Ultimately dogs treated with medical management for cataracts will eventually become blind, however these animals can still lead happy lives with minimal complications. One study compared the complications that arose in dogs with cataracts that were medically managed versus those who underwent phacoemulsification surgery. [7] The study showed no significant difference in complications between the two groups. [7]

Cataract surgery is considered an elective procedure. Surgery is the only option that removes cataracts. Not all dogs with cataracts are good surgical candidates. [1,2] Candidate selection is based on a number of factors, including but not limited to: stage of the cataract, retinal health, systemic health of the animal, and concurrent ocular disease. [1] While there is significant debate as to what stage of cataract is the best for surgery, many ophthalmologists advocate for surgery during the immature phase as there is less lens induced uveitis and the surgery is easier to perform at this stage. However, surgery can be performed when the cataract is mature. Some indications for cataract surgery include decrease vision associated with cataracts, decreased quality of life associated with vision loss, and rapidly progressive cataracts.

[2] The patient's quality of life is one of the most important factors to take into consideration for this elective procedure.

Phacoemulsification is the surgical procedure of choice for veterinary ophthalmologists. [1,2] Phacoemulsification is the procedure by which an incision is made at the limbus and the phacoemulsification probe is inserted. [1] The probe then begins to form a groove in the lens using ultrasound waves. [2] Ultrasound waves are used to shatter the lens. [1] The area is irrigated, and lens fragments are removed with aspiration. [1] Removal of all pieces of the lens is very important as it decreases post-operative inflammation, helps with placement of the intraocular lens, and decreases capsular distortion. [2] The lens capsule and anterior chamber are expanded with viscoelastic. This expansion allows space for the intraocular lens to be placed. [2] Synthetic intraocular lenses are placed in the lens capsule. Most synthetic lenses are made of acrylic or PMMA. Placement of intraocular lenses is done so to give the animal focused vision which would not be obtainable without the lens. [1] While this is typically recommended for good candidates, this is an elective procedure.

Pepper underwent phacoemulsification surgery in both eyes and had acrylic intraocular lenses placed in both eyes.

Expected Outcome and Prognosis

Canine cataract surgery has an 85-95% success rate. [2] Outcome depends on the stage of cataract at surgery and long-term postoperative checks that are performed religiously. Right after cataract surgery some complications to be aware of are things like intraocular hemorrhage, infection, corneal ulceration, fibrin formation, post-operative ocular hypertension, uveitis, and surgical site leakage. However, complications of cataract surgery can occur months to years after

surgery. The most serious complications include uveitis, retinal detachment, and secondary glaucoma. [1,2] One study showed that Labrador retrievers were at a higher risk for glaucoma, post-operative hypertension and blindness. [5] This same study showed that Labradors that had post-operative hypertension were at increased risk of developing glaucoma. [5]

Pepper had a minor iris prolapse at the incision site. She also had a small amount of iris hemorrhage. The surgeons returned the prolapse with the help of an iris spatula and viscoelastic, as well as an intracameral injection of Miostat (glaucoma medication). She had a mild increase in intraocular pressures post op that was controlled with dorzolamide/timolol ophthalmic solution. One week follow up ophthalmology exam had normal pressures and normal tear production. She had normal vision in both eyes. Her globe was also normal. Her left pupil was dyscoric and she had trace flare in her anterior chamber in that same eye. One month follow up showed normal pressures in both eyes, normal Schirmer tear test, and no stain uptake in either eye. She is doing well at home and has not had any complications.

Conclusion

Hereditary cataracts are one of the most common cataracts seen in veterinary medicine. Breed, age of onset, and location of the cataract on the lens can all be indications that these cataracts are hereditary. Pathogenesis of hereditary cataracts is poorly understood with more research needed. Phacoemulsification surgery is the surgery of choice for treating cataracts. Long term post-operative check-ups are necessary to monitor for complications, as they can arise years later.

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