Equine Recurrent Uveitis and the Cyclosporine Implant

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Introduction

Equine recurrent uveitis (1) is a spontaneously occurring disease characterized by repeated episodes of intraocular inflammation. It is also the most common cause of blindness in horses. Historically called "moon blindness" due to the believed occurrence with difference phases of the moon (2, 3), the disease has been reported to be prevalent in 2-25% of horses in the United States. (3, 4) ERU has also been referred to as iridocyclitis and periodic ophthalmia. (4) The disease has economic impacts on the horse industry as it has a high prevalence across racing breeds and Appaloosas, (5) Clinical presentation and severity of disease may vary drastically, with some horses presenting acutely with mild blepharospasm and pain, while others with more chronic disease may be bilaterally blind. The disease is progressive and is one that must be closely monitored by a veterinarian, or may require the attention of a specialized ophthalmologist.

History and Presentation

Taking a thorough history to document each previous episode of inflammation is important in diagnosing ERU. An owner report of previous brief episodes of ocular pain or swelling is highly suggestive of ERU. (2) If the history is unknown, but there is a strong suspicion of ERU, a minimum of three signs of disease in combination with some history of recurrent ocular disease must be present before diagnosing ERU. (2) While there is no specific age of onset for the disease, initial uveitis episodes in horses with ERU typically occur around 4 to 6 years (4).

Clinical presentation of ERU can vary and may be bilateral or unilateral. At times one eye may initially become inflamed while the other eye becomes involved later. Inflammation can also be present in one eye. Horses with unilateral ERU for 2 or more years with no inflammation in the other eye have a reduced chance of that eye developing ERU .(2) One study found that of

horses presenting still visual, 55% had unilateral disease while 45% had disease bilaterally. (6) In the same study, of horses that were blind, 66% had one eye affected while 34% were bilaterally blind. (6) In horses seropositive for *Leptospira pomona,* 48% had unilateral ERU while 52% had bilateral disease. (2)

Horses presenting with ERU in its classic and acute form often present with pain, blepharospasm, lacrimation, chemosis, aqueous flare, hypopyon, hyphema, miosis, and corneal changes. (2, 3) While severity of the signs may vary from horse to horse, very painful horses can present with a closed eye, making ocular examination difficult and requiring the need for sedation. Keratic precipitates may also be present on the endothelium of the cornea.

Miosis is a cardinal sign of an active uveitis. (2) The iris may have a dull color, change in pigmentation, or fibrosis. Horses with insidious ERU (discussed below) will not appear painful but may have signs of chronic inflammation like a hyperemic conjunctiva and episclera. The hallmark of insidious ERU is degeneration of the corpora nigra. (2)

Pathophysiology

ERU arises from inflammatory cells invading the uveal tract. The uvea consists of three components: the iris, ciliary body (anterior uvea), and choroid (posterior uvea). The uveal tract is very vascular and is a key component of blood supply to the eye. (3) It has proximity to peripheral vasculature, giving any systemic infection the potential to invade the uveal tract. (7) A blood-ocular barrier does exist that may be divided into the blood-aqueous barrier (iris and ciliary body) and a blood-retinal barrier (choroid). Large molecules are prevented from entering the eye due to these barriers, however, disruption of the barrier allows for blood products and other cells to leak into the eye, activating immune responses. (3)

Bacterial infections of *Escherichia coli, Rhodococcus equi, Borrelia burgdorferi,* and *Streptococcus* equi have been considered as possible causes of infection. (3, 8) Suggested viral causes include equine influenza, equine herpesvirus 4, equine arteritis virus, and equine anemia .(5) Infection with *Leptospira* may also be possible. (2, 5, 9, 10)

There is a risk between breed and development of uveitis. Appaloosas are at a much higher risk than other breeds for development of the disease (3) and are at an increased risk of becoming blind over other breeds. (11) Generally however, ERU is considered to be an autoimmune disease. This assumption comes from the known prevalence of $CD4^+$ T cells, increased interleukin 2 (IL-2) and interferon-ϒ (IFNG), and decreased IL-4 expression in ocular cellular infiltrate of ERU horses suggesting a Th1 lymphocytic mediated autoimmune disease. (10)

Once infection has taken place, first, neutrophils invade the iris and ciliary body. These neutrophils are eventually replaced by lymphocytes, plasma cells, and macrophages. (2) Concurrent changes include the arrival of fibrin and proteins. As the disease increases in prevalence, organization of lymphocytic infiltration appears. (12) This is most evident at the base of the iris and ciliary body, which begin to possess lymphocytic nodules. (2)

The epithelium of the ciliary processes and uveal vessels will thicken as the damage continues. Histopathological changes include 1) a thick, tightly adhered hyaline membrane to the nonpigmented ciliary epithelial cells 2) eosinophilic linear inclusions in the cytoplasm of the nonpigmented epithelium 3) clusters of lymphocytes and plasma cells in the nonpigmented epithelial layer of the posterior iris and ciliary body. (2, 12) In fact, finding the tightly adhered hyaline membrane to the posterior segment of the iris, combined with the presence of the linear cytoplasmic inclusion bodies in the adjacent nonpigmented epithelium is highly suggestive of ERU. (2, 12)

Chronic cases may cause changes to the retina and choroid, though most changes from ERU take place in the anterior portion of the uvea. (2, 12) The retinal pigmented epithelium may have hypertrophy or degeneration. A decrease in rods and cones can cause secondary damage to macrophage activity, destruction of the inner nuclear layer, and a detached retina. There may also be changes to the optic nerve such as lymphocyte nodule formation on the optic nerve head and cupping or swelling of the nerve itself if secondary glaucoma is present. (2) The lens may have thick exudates that adhere to the capsule in acute ERU. Over time the capsule will proliferate and cataracts develop. Anterior or posterior lens luxation is also common in ERU. (2)

During periods of remission, outwardly the eye may appear comfortable. Sequelae such as synechia, cataract development, and peripapillary scarring may be present and ultimately lead to blindness. Chronic cases may also develop phthisis bulbi while others have a normal globe size with extensive posterior syncheia, loss of normal iris shape, motility, and a dense cataract. (2)

Differential Diagnoses

ERU must be differentiated from non-ERU uveitis and other causes of persistent inflammation (i.e. keratitis, herpesvirus, glaucoma, stromal abscessation). These differentials may show clinical signs similar to those that occur in ERU such as pain, blepharospasm, photophobia, miosis, and reduced corneal transparency. (2)

Nonulcerative, deep, infectious keratitis is frequently misdiagnosed as ERU. (2) Deep stromal abscesses may come and go in their degree of severity. They can also be associated with aqueous flare, miosis, hypopyon, corneal edema, and severe pain. (2, 5) Differentiating the two is essential because treatment of one may severely worsen another. For example, treating infectious keratitis with a topical corticosteroid, which is a common treatment for ERU, may exacerbate the stromal abscess.

A group of diseases, known as “masquerading syndromes of ERU” can have disastrous consequences if not treated appropriately. (2) These diseases include non-ERU uveitis, corneal ulcers, stromal abscesses, immune mediated keratitis, herpes keratitis, corneal foreign body, corneal neoplasia, intraocular neoplasia, and glaucoma. (2) A thorough ophthalmic examination is required, with tonometry to rule out glaucoma, to differentiate these diseases. Looking for pigment changes, scarring, edema, and fundic changes can help aid in differentiation.

Diagnostic Approach/Considerations

ERU may only be diagnosed when signs of uveitis are paired with a documented history of recurrent inflammation. (4) Therefore, ERU is not diagnosed after one episode of inflammation. Performing a complete blood count (CBC) and chemistry may be useful in assessing overall health status of the horse. A conjunctival biopsy and serology for bacterial and viral agents may also be helpful in determining etiology of disease. (4) Gilger and Michau (4) recommend these steps in instances where the inciting agent has not been identified. Once a definitive agent has been identified, treatment is aimed at eliminating the primary cause.

Clinical signs of ERU necessary for diagnosis include corneal edema, aqueous flare, posterior synechia, corpora nigra atrophy, iris darkening, vitreous degeneration, and cataract formation. (4) These clinical signs in combination with a verified, documented history of persistent or recurrent episodes of uveitis is diagnostic for ERU.

Equine uveitis, once diagnosed can be classified as primary or recurrent. If recurrent, ERU can be classified as classic ERU, insidious ERU, and posterior ERU. (2, 5) Classic ERU is the most common form and is characterized by active inflammatory episodes followed by periods of

minimal observable inflammation, with each flare up of inflammation showing an increase in severity. (3) Insidious ERU is characterized by a persistent low-grade inflammation without any obvious signs of discomfort. It has a gradual destructive effect that will eventually lead to irreversible damage to ocular structures. Insidious ERU is commonly seen in Appaloosas and Draft breeds. (3, 5) Finally posterior ERU occurs primarily in the vitreous, retina, and choroid. Clinically, horses with posterior ERU will present with vitreal cloudiness, retinal detachment, vitreal inflammation, and loss of vision. Over time the horses may develop cataracts, retinal degeneration, and vitreal degeneration. Breeds commonly afflicted with posterior ERU include Warmbloods, Draft breeds, and European breeds. (3, 5)

ERU is also categorized based on degree of chronicity. It may be labeled as active/acute, quiescent, and end-stage. (2) If a horse is in an acute or active stage, observable signs of pain and inflammation will be present. These signs may include aqueous flare, corneal edema, hypopyon, miosis, iris hyperemia, and more. Horses in the quiescent phase will have little active inflammation, but may have evidence of chronic inflammation like synechia or cataracts. End-stage disease animals will present with changes that are severe such as phthisis bulbi, dense cataracts, luxated lens, and detached retinas causing vision loss. (2)

Treatment and Management Options

Therapeutic goals in treating ERU rely upon reducing inflammation and reducing discomfort. Discomfort is reduced via mydriatic cycloplegics such as atropine while corticosteroids and topical or systemic NSAIDs are used to decrease inflammation. (4) Topical corticosteroids (like prednisolone acetate 1% and neomycin-polymixin-dexamethasone) are commonly used. Potential side effects include the possibility of potentiating corneal infections and delaying epitheliazation of corneal ulcers. (4) Systemic therapy including dexamethasone or prednisolone

may be used in severe cases that are not responding to other anti-inflammatories. High-end doses of NSAIDS such as flunixin meglumine (1.1mg/kg PO or IV then decreased to 0.25mg/kg) or firocoxib (0.1mg/kg) may be used. (1) Prophylaxis for gastric ulcer formation should be included with systemic NSAID treatment. According to Gilger and Michau (13) initial therapy should be for 2 weeks, then slowly tapered off over another 2 weeks after resolution of clinical signs. A subpalpebral lavage (SPL) catheter can be placed to deliver topical medications.

In cases where *Leptospira* is suspected as the causative agent, a 4-week course of systemic tetracycline or doxycycline can help minimize or eliminate recurrent uveitis episodes. (4) Gentamicin injections into the vitreous cavity may also be useful. (4) Enrofloxacin may also be used as ocular concentrations have been shown to be above the minimum inhibitory concentration (MIC) once the blood-aqueous barrier has been disrupted (14).

Topical and systemic anti-inflammatories have long been the mainstay of treatment for ERU, however, sustained release implant devices have also come into favor. Specifically, Cyclosporine A (CsA) has been used because of its ability to specifically block interleukin-2 (IL-2). (15) With lowered IL-2 production, T-cell activation is decreased, thereby leading to overall immune suppression. Topical application of CsA has proven to be ineffective at penetrating the cornea because cyclosporine is hydrophobic. (2) Therefore, a suprachoroidal sustained release device was developed to allow slow, long-lasting release of CsA in patients with ERU.

CsA implant devices were first shown to produced a sustained level of CsA in ocular tissues of rabbits. (4) Patients must be free of active inflammation at the time of surgery to be suitable. In addition, horses that have actively inflamed eyes that are not able to be controlled with anti-inflammatories are not suitable candidates for surgery. (4) Inflamed eyes are avoided because they lead to more surgical complications.

The patient is placed under general anesthesia for suprachoroidal implantation of the CsA implant. Post-operative medications typically include flunixin meglumine and triple antibiotic ointment. It may take up to 30-45 days after the implantation for adequate levels of CsA to build up. If flare-ups occur, management with systemic NSAIDs, topical steroids, or atropine is recommended. (4, 16)

It is noted that a vitrectomy, a technique from human medicine, is another surgical option. In human medicine, the goal of this technique is to clear the vitreous of inflammatory agents rather than eliminate recurrent inflammatory episodes. (4) The removal of T cells and organisms from the vitreous theoretically decreases the initiation of recurrent flare-ups. (4) This procedure is mostly used in Europe for horses with posterior uveitis and *Leptospira* infections. (1)

Expected Outcome and Prognosis

If there is ever suspicion of ERU, owners should receive a frank discussion about prognosis and outcome. This discussion should include possibilities for visual outcome, treatment options, and expectations of frequent flare-ups. Overall prognosis for sight in ERU affected horses is poor. (2) Appaloosas are at an increased risk of blindness due to genetic predilection for disease. (5, 7) Frequent rechecks should be recommended and referral to a board certified ophthalmologist may be necessary for surgical treatment options and more advanced management.

A study examining the long-term effect of the suprachoroidal CsA implant in ERU horses found among ranges of 13-85 months post surgery, 78.8% of eyes were visual. (17) Complications eventually leading to vision loss included uveitis episodes, glaucoma, cataracts, and retinal detachment. Overall the prognosis for ERU with the CsA implant is greatly improved over medical management and should be considered in appropriate horses.

Other Pertinent Information

There is a known association between Leptospirosis and ERU. (2, 7, 9, 10) *Leptospira* are thin, motile spirochetes that appear in regions with a mild climate, high precipitation, and flood-prone areas. Horses are accidental hosts of leptospirosis and become infected after drinking contaminated water containing urine from a carrier species. A 7-9 day period of bacteremia characterized by pyrexia occurs after initial exposure. (2) An antibody response then follows allowing organisms to be cleared from the bloodstream. (3) Although the infection is cleared, horses may shed the bacteria in their urine for up to 5 months. (18) Although the antibody response peaks at 14 days, antibodies may be detected for up to 7 years after infection. (18)

Diagnosing leptospirosis induced uveitis may be difficult but is usually done by antibody detection in serum and ocular fluids via microscopic agglutination tests (MAT). (9) Polymerase chain reaction (PCR) protocols have also been used for diagnosis of ERU. (2, 9, 18) In the southeastern United States, one 2014 study found that 21% of horses diagnosed with ERU cultured *Leptospira.* (9) They also found that horses seropositive for *Leptospira* were more likely to have the serovars *pomona* and *grippotyphosa* and thus concluded that these two serovars are involved in the pathogenesis of ERU. (3, 9) Systemic antibiotics with good ocular penetration (such as enrofloxacin) were useful in treating early stages of disease. (9)

Conclusion

In conclusion, ERU is a progressive disease that may cause bilateral loss of vision in affected horses. Appaloosas are genetically predisposed to disease development and vision loss. While anti-inflammatories are the medical mainstays of treatment, implantation of CsA sustained release devices has been shown to control flare-ups in suitable horses. If disease progression is

severe enough, referral to a board certified ophthalmologist is recommended with consistent rechecks to optimize each animal's visual prognosis.

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