REVIEW DERLEME

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Ocular Findings of Systemic Diseases in Dogs: Traditional Review

Köpeklerde Sistemik Hastalıkların Oküler Yansımaları: Geleneksel Derleme

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ABSTRACT There are many systemic diseases in dogs that have the potential to cause major changes in the eye due to its hypersensitivity to external factors and conditions. Taking all of this into consideration, the eye has a significant contribution to make to the veterinarian in the diagnosis of systemic diseases in dogs and in the management of these diseases. It is also possible to reach a diagnosis of a systemic disease after ophthalmologic examination in patients brought to the clinic with eye symptoms. In addition, regular ophthalmic examinations in animals with systemic disease can prevent potential complications and provide an idea of the prognosis of treatment. While there are diseases that cause sudden blindness, such as Sudden Acquired Retinal Degeneration Syndrome and immune-mediated retinitis, there are also eye diseases that develop more slowly due to infectious diseases. Agents such as *Brucella canis, Aspergillosis* spp*., Dirofilaria immitis, Leishmania infantum, Ehrlichias*pp., canine distemper virus and Canine Herpesvirus can cause infectious diseases that may present with ophthalmological findings. Endocrine system disorders (diabetes mellitus, hyperadrenocorticism, hypothyroidism), congenital disorders (Ehlers-Danlos syndrome, hydrocephalus), various drug toxicities (ivermectin toxicity, anticoagulant rodenticide toxicity) and developmental disorders (ceroid lipofuscinosis and GM1 gangliosidosis) may cause ophthalmological damage. The most common ocular manifestation of these diseases is uveitis. The aim of this review is to provide information on the ophthalmological findings of common systemic diseases and their treatments in dogs.

Keywords: Congenital; developmental; dog; eye; infectious

ÖZET Köpeklerde birçok sistemik hastalıkların gözde önemli değişimlere sebep olabilme potansiyeli bulunmaktadır. Bunun sebebi, gözün dış faktörlere ve hastalıklara karşı oldukça duyarlı olması ileilişkilendirilmektedir. Göz, tüm bu özellikler dikkate alındığı zaman, köpeklerde sistemik hastalıkların teşhisinde ve bu durumların tedavilerinin seyrinde veteriner hekimlere önemli katkılar sunmaktadır. Göz bulguları nedeniyle kliniğe getirilen hastalarda oftalmolojik muayenenin gerçekleştirilmesinin ardından sistemik bir hastalığın teşhisine de ulaşabilmek mümkündür. Ayrıca sistemik bir hastalığı bulunan köpeklerde periyodik göz muayenesi yapılarak oluşabilecek potansiyel komplikasyonlar önlenebilir ve tedavinin prognozu hakkında bilgi sahibi olunabilir. Ani Gelişen Retina Dejenerasyon Sendromu ve immün kaynaklı retinit gibi ani körlükle ortaya çıkan hastalıklar olduğu gibi enfeksiyöz hastalıklara bağlı daha yavaş gelişen göz hastalıkları da vardır. *Brucella canis, Aspergillus* spp*., Dirofilaria immitis, Leishmania infantum, Ehrlichia* spp., canine distemper virüs ve canine herpes virüs gibi etkenler oftalmolojik bulgularla seyredebilen enfeksiyöz hastalıklara yol açabilmektedir.Endokrin sistem bozuklukları (diabetes mellitus, hiperadrenokortisizm, hipotiroidizm), kongenital hastalıklar (Ehlers-Danlos sendromu, hidrosefalus), çeşitli ilaç toksikasyonları (ivermektin toksikasyonu, antikoagülan rodentisit toksikasyonu) ve gelişimsel hastalıklar (seroid lipofusinozis ve GM-1 gangliosidoz) oftalmolojik hasara neden olabilmektedir. Üveit, köpeklerde bu bozuklukların seyri sırasında en fazla gözlenen oftalmolojik bulgudur. Bu derlemede, köpeklerde yaygın olarak görülen sistemik hastalıkların oluşturduğu oftalmolojik bulgular ve bunların sağaltımı hakkında bilgi verilmesi amaçlanmıştır.

Anahtar Kelimeler: Kongenital; gelişimsel; köpek; göz; enfeksiyöz

Systemic diseases in dogs can present with a variety of ocular findings. Ocular findings not only aid in the early and accurate diagnosis of systemic disease but also help to evaluate treatment more effectively. Ophthalmoscopy in dogs with systemic disease is an essential part of the diagnostic process as it reduces the number of differential diagnoses.

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ACQUIRED DISEASES

ANEMIA

In severe anemia, pale retinal vessels, varying degrees of retinal hemorrhages, and marked changes in the tapetal reflex may be seen. Retinal hemorrhages are more likely to be seen and may be more severe if associated with thrombocytopenia. Small intraretinalhemorrhages are typical and may resolve rapidly with correction of the anemia, but pigmentary defects may remain in the retina.[1,2]

SUDDEN ACQUIRED RETINAL DEGENERATION SYNDROME

Sudden Acquired Retinal Degeneration Syndrome (SARDS) is an acquired and idiopathic disease that causes acute blindness with no fundus changes in the early stages, but as the disease progresses a variable degree of retinal vascular attenuation and tapetalhyperreflectivity may be seen, reflecting the ongoing process of retinal degeneration.[3,4] Animals characteristically present with acute blindness with a normal or near normal fundus. Because of the acute nature of the disease, most dogs will have an irregularity in movement. In most patients, vision loss develops within 1-2 weeks and nyctalopia may also be observed. The average age of onset is 8.5-10 years. On ophthalmological examination, dogs with SARDS are blind and have a positive dazzle reflex but no threatening reflex. The pupils are usually dilated and the pupillary light reflex response is weak.[5] Ophthalmoscopic changes in the acute phase are minimal, consisting of moderate retinal vascular regression or moderate changes in retinal vessel diameter and tapetal reflectance. All dogs with SARDS have a characteristic pallor of the optic disc in the early stages. Typically, tapetalhyperreflexia foci, which are not very prominent, can be seen in patients for more than 2 months.[6,7]

While no treatment has proven effective, SARDS in dogs has been anecdotally treated with systemic immunosuppressants, such as prednisone or leflunomide. If immunosuppressive therapy is elected, patients are reevaluated in a few weeks to months. If any improvement is seen, a discussion of long-term therapy can occur. If no improvement is seen, the patient is generally weaned off the medications.[8] Consistently successful treatments to reverse vision loss in SARDS have not been identified.[9]

IMMUNE-MEDIATED RETINITIS

Dogs with immune-mediated retinitis (IMR) typically have a sudden onset of blindness that is sporadic and occasional and may last for several months or years, especially after loss of night vision. In bright light, affected dogs may have dilated pupils and/or anisocoria. Examination of the fundus in dogs affected by IMR may show no significant findings, but a characteristic opacity of the optic disc due to vascular regression at the optic nerve head may be observed. This finding may also be seen in dogs with SARDS.[6]

These diseases can be treated with either combined topical and oral corticosteroids (prednisone, 0.5-1 mg/kg, every 12 hours) or a lower corticosteroid dose in combination with other immunosuppressive drugs.[10]

INFECTIOUS DISEASES

BRUCELLOSIS

It is a zoonotic infection of dogs caused by *Brucella canis*. *B. canis* has been isolated from the eye and corneal opacity due to anterior uveitis, chorioretinitis, panuveitis, panophthalmitis, retinal detachment, vitritis, keratoconjunctivitis, hyphema, endophthalmitis, posterior synechiae, and corneal edema has been observed in experimental and naturally occurring infections. Ocular inflammation caused by *B. canis* is usually unilateral and associated with intraocular hemorrhage. Ocular inflammation is usually chronic and progresses slowly. Approximately 14% of *Brucella* cases have ocular findings.[11,12] Brucellosis should be suspected in dogs with recurrent uveitis.[13]

Treatment of canine brucellosis requires long-term antimicrobial therapy and may not result in permanent eradication of infection. Combinations of antimicrobials for prolonged treatmentdurations must be used to maximize the chance of clearing *B. canis* infection. Of the antimicrobial combinations

reported, the most consistently efficacious in vivo has been streptomycin and tetracyclines. A combination of aminoglycoside, fluoroquinolone, and tetracycline has recently been recommended for thetreatment of brucellosis with ocular involvement.[14]

ASPERGILLOSIS

*Aspergillus*spp.is a ubiquitous opportunistic infection caused by the inhalation of spores, causing localized or disseminated disease. Disseminated aspergillosis is common in German Shepherd dogs. Although rare, it can cause ocular findings such as orbital cellulitis, ulcerative keratitis, panuveitis, chorioretinitis, exudative retinal detachment and endophthalmitis. Third eyelid elevation and hyperemia, moderate buphthalmia, peripheral corneal edema, keratitis, dysphoria, cataractandsevere unilateral/bilateral panophthalmitis with secondary glaucoma may occur.[15]

Intravitreal and/or systemic amphotericin B is commonly used to treat Aspergillusendophthalmitis, although the intraocular form may be toxic to theretina.Intravitreal amphotericin B (5 mg/0.1 mL) has been safely used. Intravitreal dexamethasone is administered to reduce intraocular inflammation but the efficacy has not been tested in studies. Oral prednisone 1 mg/kg/body weight should be used in tapering doses.[16]

OPHTHALMOMYIASIS

It is the penetration of fly larvae or eggs of the order *Diptera* into the ocular tissues of mammals. Parasitic fly species of the genus *Cuterebra* can cause this condition. Cases of ophthalmomyiasisinterna and externa have been reported in dogs. Purulent discharge from the eye may or may not be seen.[17] Indirect ophthalmoscopy of a case of ophthalmomyosis caused by *Cuterebra* spp. larvae in a 5-month-old dog showed white-colored larvae in the posterior vitreous, curvilinear subretinal folds in the intravitreal, tapetal and non-tapetal regions.[18]

For patientswith some degree of anterior uveitis anddiscomfort, medical management is often pursued until the patient is comfortable and theeye is quiet, or until the anterior chamber is translucentenough for additional procedural intervention, such askeratotomy and extraction or laser photocoagulation. In cases of mobile larvae, surgical intervention should be considered as early as possible to minimize further tissue damage from larval migration and prevent movement of the larva to regions of the globe that are less surgically accessible.[19]

DIROFILARIASIS

It is a serious and potentially fatal disease caused by the heartworm *Dirofilaria immitis*, transmitted to dogs by *Culicidae flies*. It occurs when the fourth larval stage (L4) passes from the subconjunctival space into the eye, where the larvae develop into the fifth stage (L5). In a retrospective study of 21 dogs with *D. immitis*, the parasite was found unilaterally in the anterior chamber of 20 dogs. Parasites can also be seen in the vitreous. Anterior uveitis and an increase in ocular pain may be observed when light is shone on the eye due to themovement of the parasite in the eye. Corneal edema is usually seen in chronic cases.[20] Subconjunctival ectopic dirofilariasis has also been reported in a dog.[21]

Surgical removal is the treatment of choice for intraocular dirofilariasis in dogs.[22]

LEISHMANIASIS

It is a chronic and fatal disease caused by *Leishmania infantum* and transmitted to dogs by *Phlebotomus* spp. flies. There are visceral and cutaneous forms of the disease. In addition to the systemic manifestations of the disease, ocular manifestations are common. Complications developing in the affected tissues can lead to blindness.[23] The incidence of ocular findings in leishmaniasis varies from 16-81%.[24,25] In a retrospective study of 430 dogs with leishmaniasis, ocular findings were seen in 105 dogs, 103 of which had bilateral findings. These included anterior uveitis (90%), conjunctivitis and K (66%), periocularallopia (56%), diffuse blepharitis (54%), ulcerative blepharitis (8%), posterior uveitis (8%), keratoconjunctivitissicca (KCS) (6%), orbital cellulitis (4%) and eyelid nodules (2%). Secondary glaucoma may also occur in those who develop anterior uveitis.[26]

The treatment regimen for canine leishmaniasis includes a combination of N-

methylglucamineantimoniate for a minimum of 30 days and allopurinol for 6months to 1 year. In a study, approximately 50% of the 34 cases had marked improvement or resolution of ocular signsfollowing therapy.[26]

EHRLICHIOSIS

In dogs; *Ehrlichiacanis*, *Ehrlichia chaffeensis* and *Ehrlichiaristiciiatypicalis* are the causative agents of monocyticehrlichiosis, transmitted by *Rhipicephalus sanguineous* ticks, may also be seen with other tick-borne agents. *Ehrlichiaewingii*, *Ehrlichiaequi*, *Ehrlichiaphagocytophila* and the human granulocytic ehrlichiosis agent are thrombocyticehrlichiosis agents. Ehrlichia platys causes thrombocyticehrlichiosis in dogs. Although ocular findings are common with *Ehrlichiacanis*, they may not be seen in all patients. Common ocular findings include conjunctival and episcleral hyperemia, miosis, aqueous flare, hypopion, keratic precipitates, hyphema, synechiae and hypotony with unilateral/bilateral anterior uveitis. One or more of these findings may occur simultaneously. Glaucoma may occur as a result of anterior uveitis. Posterior segment inflammation may present as chorioretinitis, severe retinal detachment, retinal hemorrhages and optic neuritis. Inflammatory perivascular retinal infiltrates, retinal hemorrhages and necrotizingscleritis may develop. In a study of 88 dogs with *Ehrlichiacanis*, uveitis alone (iridocyclitis, posterior uveitis and panuveitis) was found in 63, and uveitis and secondary glaucoma in 22. Crusty eye (45.4%), episcleral congestion (69.3%), ciliary redness (28.4%), corneal edema (61.3%), keratic precipitate (18.1%), aqueous flare (22.7%), hyphema (10.2%), iris edema (36.3%), rubeosisiridis (25%), iris pigmentation and retinal detachment (11.3%), retinal vascular folds (27.2%), hemorrhages (12.5%) and retinal hyperreflexia (9%) have been reported.[27]

In a retrospective study of 90 dogs with *Ehrlichiacanis*, ocular findings were observed along with other clinical signs, but only ocular findings were noted in 30 dogs. The most common findings were unilateral (22/90) or bilateral (68/90) uveitis classified as anterior (58, 64.5%), posterior (8, 8.9%) and panuveitis (24, 26.6%). Corneal ulcer (12/90, 13.3%), necrotizing scleritis (10/90, 11.1%), decreased tear production (8/90, 8.9%) and orbital cellulitis (3/90, 3.3%) were also noted. Due to its negative effect on tear production, it causes corneal dryness and secondary bacterial infections. As a result, deep corneal ulcers can occur.[28]

Anterior uveitis was seen in a dog infected with *Ehrlichiachaffeensis*. Necrotisingscleritis causes severe destruction of intraocular structures.

Little is known about the ocular manifestations of granulocytic ehrlichiosis. Dogs with high titers of *Ehrlichiaequii* have had anterior uveitis or chorioretinitis with severe retinal detachment, and most have no evidence of systemic disease. Although rare, uveitis has been reported in *Ehrlichia platys* infection. Dogs with high titers of *Ehrlichiaequii* have had anterior uveitis or chorioretinitis with severe retinal detachment, and most have no signs of systemic disease. No ocular findings have been reported with *Ehrlichia ewingii*.[29]

Doxycycline (5 mg/kg twice daily for 21 days) has become the standarddrug for treating canine rickettsial infections. In chronic or refractory cases, imidocarbdipropionate (5 mg/kg intramuscular) or doxycycline treatment oflonger duration (2-3 months) can be used. In anterior segmentocular inflammatory lesions, topical 0.1% dexamethasone solution; in uveitis, cycloplegia/mydriatic therapy, and for secondary glaucoma, antihypertensive agents can be used.[30]

DISTEMPER

It is caused by canine distemper virus of the genus *Morbillivirus*, family Paramyxoviridae. Conjunctivitis, oculonasal and periocular discharge are observed.[31,32] Chorioretinitis is commonly reported. Fundus lesions are usually seen in the peripheral and mid-peripheral non-tapered fundus. Acute retinitis, characterized by congestion and perivascular deposits in the retinal vessels, may lead to retinal edema. On ophthalmoscopy, these lesions can be seen as a grey opacity around the retinal vessels. Hyperreflective and depigmented areas in the tapetal fundus indicate that the dog may have had distemper. One of the most prominent findings in these infections is optic neuritis. Retinal edema

around the disc can lead to retinal detachment. Blindness may be seen with mydriasis or a slow/negative pupillary light reflex.[33] Canine viral diarrhea causes severe retinal detachment, often with chorioretinitis and loss of vision, during the acute phase of infection or several years after infection.[34] Optic nerve swelling and bilateral peripapillaryedema may be seen.[35] It is often associated with permanent or temporary KCS.[36]

Ocular treatment, which is essentially symptomatic, consists of topical ophthalmic antibacterial preparations for conjunctivitis and corneal ulcers. Cases of KCS may be treated with artificial tears, topical antibiotics and lacromimetics. Treatment of severe corneal ulceration may require surgical intervention. Systemic and topical steroids as well as topical atropine are indicated in cases of uveitis. However, atropine should be used with extreme caution if the animal is also suffering from KCS, and steroids may not be used if the cornea is ulcerated. Systemic administration of antiinflammatory dosages of glucocorticosteroids is indicated in an animal with acute optic neuritis following confirming thediagnosis of distemper, even if there is no other sign of clinical disease.[37]

CANINE HERPESVIRUS

It is caused by the canine herpes virus 1 (CHV-1) of the Herpesviridae family.[38] It is a fatal generalized necrotizing and hemorrhagic disease in puppies of 1-2 weeks of age. Adult dogs over 2 weeks of age are usually asymptomatic. In older dogs, it affects the upper respiratory tract.[39] Keratitis, peripheral anterior synechiae, cataracts, optic neuritis, retinal necrosis and retinal dysplasia may develop. Visual impairment or blindness is common. Although the lesions are usually bilateral, they are not always symmetrical in severity. The immune status and age of the dog influence the occurrence of ocular findings in both cases. In immunocompromised adult dogs, ocular lesions are more severe and persist for longer. Unlike fetal and neonatal dogs, ocular lesions in adult dogs occur on the ocular surface and accessory organs of the eye and include blepharitis, conjunctivitis, ulcerative keratitis and non-ulcerative keratitis. Common ocular lesions are; blepharospasm, photophobia, ocular pruritus, third eyelid elevation and ocular discharge. The earliest finding is epiphora, as the disease progresses the discharge becomes mucoid, mucopurulent or serosanginous. Miosis is often seen in ulcerative or non-ulcerative keratitis. Focal or diffuse blepharitis may be seen. In focal blepharitis, the inferonasal region of the lower eyelid is most commonly affected. Blepharitis manifests as erythema, edema, exudate, crusting, ulceration and areas of alopecia. Conjunctivitis is the most common finding in adult dogs and can be seen in isolation or with eyelid and corneal problems. Symptoms of conjunctivitis may include conjunctival hyperemia, schemosis, ocular discharge and ocular pain. In addition to these non-specific clinical symptoms, conjunctival petechial hemorrhages and conjunctival epithelial ulcers may develop. Ulcerative keratitis (dendritic ulcer) is a common lesion in adult dogs, in contrast to non-ulcerative keratitis.[40,41]

The goals of therapy for ocular CHV-1 infection are to shorten the disease course, reduce discomfort, limit viral shedding into the environment, and prevent severe complications. An Elizabethan collar is indicated in most cases to prevent self-trauma. All dogs should receive a topical ocular antimicrobial to prevent secondary bacterial infection which can complicate therapy and lead to severe ocular sequelae such as corneal perforation. Topical ocular atropine administered to effect (to achieve mydriasis) improves comfort in dogs with corneal disease. Successful topical ocular antiviral therapy with idoxuridine 0.1% ophthalmic solution, trifluridine 1% ophthalmic solution and cidofovir 0.5% ophthalmic solution is described in clinical reports of dogs with CHV-1 infection.Compounded cidofovir ophthalmic solution is an alternative therapy reported for CHV-1 ulcerative keratitis. It is reported to be effective in dogs with CHV-1 ocular disease with twice daily administration; however, the incidence of adverse reactions may be higher than with the other reported topical antivirals. Oral antiviral therapy is not reported for dogs with ocular CHV-1 infection and effective medication dosages are unknown; however, pharmacokinetic studies for some medications (e.g. acyclovir and famciclovir) that have therapeutic potential are described in dogs.[40]

INFECTIOUS CANINE HEPATITIS

It is a multisystemic disease caused by canine adenovirus type 1 (CAV-1). In addition to natural infection, interstitial nephritis and ocular disease can occur as a result of vaccination with a modified live virus.[33] Following vaccination of 243 dogs with live CAV-1 virus, ocular lesions were detected in 0.4%.[42] The characteristic ocular lesions of CAV-1 are corneal edema and iridocyclitis. Pupil miosis, iris opacity and sometimes thickening, decreased intraocular pressure, aqueous flare and hypopion may be observed. Although the associated pain or discomfort usually subsides when the corneal opacity is at its greatest, uveitis may rarely persist. Corneal opacity is typically diffuse and has a specific mottled appearance. An increase in corneal thickness may be observed. It can lead to keratoconus by deforming the curvature of the cornea due to edema in the corneal stroma. Corneal disorders can heal quickly. After recovery, glaucoma may develop due to CAV-1-induced uveitis. Buphthalmia can develop rapidly in puppies with glaucoma.[33] Approximately 20% of recovered dogs may develop corneal opacity ("blue eyes") after 2-3 weeks due to the accumulation of immune complexes in one or both eyes.[39] "Blue eyes" are usually temporary and the corneal opacity may resolve in a few days. In rare cases, the condition can last longer and cause severe eye reactions and permanent vision problems.[43]

Treatment of dogs with acute infectious canine hepatitis is purely supportive and consists primarily of fluid therapy, including crystalloid fluids and blood products. Other medications that may be indicated include antiemetics, antacids, sucralfate, whole blood or plasma transfusions and colloids suchas hetastarch. After fluorescein staining has shown no evidence of corneal ulceration, dogs with severe corneal edema and uveitis should.

DIABETES MELLITUS

It is an endocrine disease caused by insufficient or absent production of insulin by the pancreas. The eyelids, conjunctiva, cornea, uvea, lens and retina may be affected. Uveitis and KCS may occur. The cataract begins with the formation of vacuoles in the equatorial region of the lens.[45] It may also cause bilateral Horner's syndrome.[46] In a retrospective study of 20 dogs with diabetes mellitus (DM), spontaneous rupture of the lens capsule was found in 30 of 40 eyes with bilateral cataracts. The location of the rupture was equatorial in 29 and posterior in 1.[47] Diabetic dogs have a marked reduction in corneal sensitivity and diabetic retinopathy. Lipemiaretinalis, retinopathy, retinal hemorrhages, retinal detachment and hyphema may develop.[48] Many systemic complications, including diabetic cataracts and retinopathy, can lead to blindness. Cataract formation is the most common ocular complication. Lens proteins elicit an inflammatory response when leakage from the lens capsule occurs, known as lens-induced uveitis (LIU), and occurs in up to71% of patients with cataracts. Concurrent DM and KCS have been documented in dogs as well as in humans.[45] A recent publication reported ocular surface changes in DM, including reduced tear production in 15 diabetic dogs.[49]

Diabetic dogs may undergo surgical treatments to restore vision secondary to diabetic cataracts like phacoemulsification and intraocular lens implantation. Cataract surgery in dogs is often not recommended until cataractsreach an immature to mature stage. Due to the high prevalence of LIU associated with cataracts, topical or systemic anti-inflammatory therapy should be considered. Medical therapy for DM-related cataracts before onset or in early stages using an aldose reductase inhibitor has shown success in prevention or slowed progression. No treatment for diabetic retinopathy is currently recommended. The use of tear stimulants such as topical cyclosporine or compounded versions of cyclosporine and tacrolimus should be considered when faced with low tear production in a diabetic canine patient. Such drugs not only boost tear production but suppress inflammation by inhibiting of the expression of inflammatory cytokines and chemokines, thereby promoting corneal epithelial health.[45]

HYPERADRENOCORTICISM (CUSHING SYNDROME)

It is one of the most common endocrinopathies in dogs. It usually affects animals over six years of age. Clinical and laboratory findings occur as a result of chronic glucocorticoid excess or, less commonly,

overproduction of adrenal androgens. Progressive corneal ulceration, non-healing corneal ulcer, corneal calcification and lipid deposition, cataract, KCS, retinal lipemia, retinal hemorrhages, retinal detachment, hyphema, lipemic aqueous humor, blindness, oculomotor paralysis, ptosis, uveitis, endophthalmitis, opportunistic infections, keratitis, endophthalmitis, band keratopathy, eyelid protrusion and SARDS.[50,51]

Dogs may be treated using the adrenolytic agent mitotane, beginning with an induction dosage of 25-50 mg/kg/day for 7-10 days. Treatment of iatrogenic hyperadrenocorticism should include a change to an oral, short-acting steroid such as prednisone or prednisolone.[52]

HYPOTHYROIDISM

It is a syndrome that develops with a deficiency of the active thyroid hormones triiodothyronine (T3) and thyroxine (T4).[53] As a result of hyperlipidemia, corneal lipidosis, lipid accumulation in the aqueous humor and retinal lipemia may develop. Facial paralysis as a result of peripheral neuropathy, keratitis due to permanent open eye, and Horner's syndrome may develop.[51] KCS and lipid corneal dystrophy, corneal ulcer, uveitis, conjunctival congestion, hyperemia, retinal detachment and retinal hemorrhages may be seen.[54] As a result of cranial nerve dysfunction in vestibular disorders, findings such as nystagmus, strabismus andfacial nerve paresis/paralysis may occur.[50,53]

Canine hypothyroidism can be adequately treated in the vast majority of cases with oral levothyroxine therapy administered once daily. A mean starting dose of 0.02 mg/kg is adequate in most dogs.[55]

HYPOCALCEMIA

Hypocalcaemia may cause ocular abnormalities such as cataracts, third eyelid prolapse, optic neuritis, papilledema, conjunctivitis, keratitis, strabismus, nystagmus and anisocoria.[51]

CENTRAL NERVOUS SYSTEM TUMORS

It can be seen as blurred vision, bumping of surrounding objects, bilateral negative threat reflex, dilation of the pupils in both eyes and a slight combing of the pupil margins consistent with senile iris atrophy. Weak pupillary light reflex, bilateral pupillary sclerosis and incipient anterior cortical cataract of the lens may be seen.[56] In addition to neurological findings, papilledema and visual disturbances are common in intracranial neoplasms. Primary or secondary intracranial neoplasms usually present with ocular and/or orbital findings. Acute blindness may also occur with intracranial tumors. In diffuse or multifocal cases, neurological findings may be associated with blindness. Blindness may occur in the absence of neurological findings in masses affecting only the periphery of the optic chiasm. Non-functioning pituitary carcinomas, optic nerve gliomas and meningiomas may involve the optic chiasm.[50]

In gliomas, the prognosis is good if the neoplasm is completely excised, as the metastatic potential is low. On the contrary, if the tumor extends to the optic nerve margin, invasion of the remaining optic pathways into the ventral brain is possible.[57]

IVERMECTIN TOXICITY

Ivermectin toxicity occurs particularly in collie breeds as a result of a mutation in the multidrug resistance 1 gene. Sudden blindness, slowing of the pupillary light reflex in both eyes and mydriasis, multifocal retinal edema, folds and mild retinal detachment may be seen.[58] Choroidal hypoplasia and coloboma may develop in the optic disc or adjacent areas.[59]

Treatment with an infusion of intravenous lipid therapy appeared to shorten the clinical course of thedisease in this patient without affecting electroretinography results.[60]

ANTICOAGULANT RODENTICIDE TOXICITY

Ocular findings are dominant in anticoagulant rodenticide toxicity. Bilateral epiphora, severe diffuse subconjunctivalhemorrhages, miosis, elevation of the third eyelid, superficial corneal ulcer, exophthalmos, lagophthalmus, decreased retropulsion, pain on palpation (head, orbit and around the mouth) and blindness may occur.[61] Hyphema and petechial hemorrhages in the conjunctiva have been reported.[62]

Treatment for anticoagulant rodenticide toxicity consists of oral administration of vitamin K1 for 2-4

weeks depending on which rodenticide is ingested. Cases with severe hemorrhaging may require fresh frozen plasma transfusions to provide adequate coagulation factors.[63]

CONGENITAL DISEASES

EHLERS-DANLOS SYNDROME (CUTANEOUS ASTHENIA)

It is a congenital, inherited syndrome characterized by fragility and tearing of the skin. When the full syndrome develops, ocular lesions such as eyelid drooping, corneal edema, thinning of the sclera, cataract, bilateral lens dislocation and diffuse corneal cataract may occur.[64]

Systemic steroids (betamethasone dipropionate) and a diuretic (dichlorphenamide) can be given together with an analgesic (buprenorphine).[65]

HYDROCEPHALUS

It is an increase in the amount of cerebrospinal fluid (CSF) inside the skull. Ventrolateral strabismus is common in congenital hydrocephalus due to the pressure of the skull on the dorsolateral region of the orbit. This causes the eyes to be pushed to the ventrolateral side, resulting in a "sunset" image on the cornea. Ventrolateral strabismus can also occur as a result of cranial nerve damage. Rarely, papilledema may also occur.[13]

Diuretics are used to reduce the production of CSF. Acetazolamide, furosemide, prednisone and omeprazole have been shown to decrease CSF production by the choroid plexus in both the dog and cat. Surgical treatment (ventriculoperitoneal shunt placement) is generally recommended when an animal is showing worsening clinical signs, shows no evidence of improvement or deteriorates when being treated medically.[66]

DEVELOPMENTAL DISEASES

CEROID LIPOFUSCINOSIS

Ceroid lipofuscinoses are a group of inherited proteinosescharacterized by the accumulation of proteins in nerve cells and other tissues, including the retina. Visual impairment, especially in dim light, is usually the first finding in ceroidlipofuscinoses. Blindness usually develops over time.[67]

Repeated periodic intravitreal injections of recombinant human tripeptidyl peptidase-1 are effective in inhibiting retinal degeneration and preserving retinal function in canine neuronal ceroid lipofuscinosis-2 form of the disease.[68]

GM1-GANGLIOSIDOSIS

GM1-Gangliosidosis is a type of sphingolipidosis found in Alaskan Huskies, English Springer Spaniels, Beagle crosses, Portuguese Water Dogs and ShibaInus. Clinical findings in this disease are: opacity in the center of the cornea in Shibainus and Portuguese Water Dogs; visual impairment in Shibainus and Portuguese Water Dogs; strabismus in Beagle crosses and Alaskan Huskies; limited to nystagmus in English Springer Spaniels, Portuguese Water Dogs and Alaskan Huskies.[69]

It is caused by autosomal recessively inherited deficiency and at present, only symptomatic therapy is available.[70]

CONCLUSION

The eye undergoes many changes during systemic disease due to its hypersensitivity to external factors and conditions. Among these, the most common ocular finding is uveitis. Ophthalmic examination in conjunction with routine physical examination of the dog allows earlier and more accurate diagnosis of systemic problems and more effective evaluation of treatment.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

REFERENCES

1. Carraro MC, Rossetti L, Gerli GC. Prevalence of retinopathy in patients with anemia or thrombocytopenia. Eur J Haematol. 2001;67(4):238-44. PMID: 11860445.
2. Shelah-Goraly M, Aroch I, Kass PH, Bruchim Y, Ofri R. A prospective study of the association of anemia and thrombocytopenia with ocular lesions in dogs. Vet J. 2009;182(2):187-92. PMID: 18664411.
3. Susanti L, Kwon D, Ahn J, Seo K, Kang S. Unilateral blindness presumed as sudden acquired retinal degeneration syndrome (SARDS) in one Dachshund and four Maltese dogs. Vet Ophthalmol. 2023;26(2):169-75. PMID: 36647151.
4. Washington DR, Li Z, Fox LC, Mowat FM. Canine sudden acquired retinal degeneration syndrome: Owner perceptions on the time to vision loss, treatment outcomes, and prognosis for life. Vet Ophthalmol. 2021;24(2):156-68. PMID: 33377263; PMCID: PMC7979495.
5. Van der Woerdt A, Nasisse M, Davidson M. Sudden acquired retinal degeneration in the dog: clinical and laboratory findings in 36 cases. Prog Vet Comp Ophthalmol. 1991;1:11-8. Kaynağa direkt erişim sağlanabilecek link bilgisi eklenmelidir.
6. Grozdanic SD, Harper MM, Kecova H. Antibody-mediated retinopathies in canine patients: mechanism, diagnosis, and treatment modalities. Vet Clin North Am Small Anim Pract. 2008;38(2):361-87, vii. PMID: 18299012.
7. Balicki I, Goleman M, Balicka A. Ocular abnormalities in Polish Hunting Dogs. PLoS One. 2021;16(11):e0258636. PMID: 34739488; PMCID: PMC8570502.
8. Colorado State University [Internet]. ©2023 Colorado State University [Cited: November 6, 2023]. Sudden acquired retinal degeneration syndrome (SARDS) in dogs Available from: https://vetmedbiosci.colostate.edu/vth/services/ophthalmology/sudden-acquired-retinal-degeneration-syndrome/
9. Stuckey JA, Pearce JW, Giuliano EA, Cohn LA, Bentley E, Rankin AJ, et al. Long-term outcome of sudden acquired retinal degeneration syndrome in dogs. J Am Vet Med Assoc. 2013;243(10):1425-31. PMID: 24171371.
10. MSD Manual Veterinary Manual [Internet]. MSD ©2023 Merck & Co., Inc. [Cited: November 6, 2023]. Available from: https://www.msdvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-eye/treatment-of-intraocular-inflammation-in-animals
11. Vinayak A, Greene CE, Moore PA, Powell-Johnson G. Clinical resolution of Brucella canis-induced ocular inflammation in a dog. J Am Vet Med Assoc. 2004;224(11):1804-7, 1788-9. PMID: 15198266.
12. Ledbetter EC, Landry MP, Stokol T, Kern TJ, Messick JB. Brucella canis endophthalmitis in 3 dogs: clinical features, diagnosis, and treatment. Vet Ophthalmol. 2009;12(3):183-91. PMID: 19392878.
13. Gelatt K, Gilger B, Kern T. Veterinary Ophthalmology. 5th ed. Ames, Iowa: Wiley-Blackwell; 2013.
14. Ledbetter EC, Landry MP, Stokol T, Kern TJ, Messick JB. Brucella canis endophthalmitis in 3 dogs: clinical features, diagnosis, and treatment. Vet Ophthalmol. 2009;12(3):183-91. PMID: 19392878.
15. Wooff PJ, Dees DD, Teixeria L. Aspergillus spp. panophthalmitis with intralenticular invasion in dogs: report of two cases. Vet Ophthalmol. 2018;21(2):182-7. PMID: 27641998.
16. Spadea L, Giannico MI. Diagnostic and management strategies of aspergillus endophthalmitis: current insights. Clin Ophthalmol. 2019;13:2573-82. PMID: 31920280; PMCID: PMC6939405.
17. Crumley WR, Rankin AJ, Dryden MW. Ophthalmomyiasis externa in a puppy due to Cuterebra infestation. J Am Anim Hosp Assoc. 2011;47(6):e150-5. PMID: 22058363.
18. Ollivier FJ, Barrie KP, Mames RN, Kallberg ME, Greiner EC, Plummer CE, et al. Pars plana vitrectomy for the treatment of ophthalmomyiasis interna posterior in a dog. Vet Ophthalmol. 2006;9(4):259-64. PMID: 16771763.
19. Edelmann ML, Lucio-Forster A, Kern TJ, Bowman DD, Ledbetter EC. Ophthalmomyiasis interna anterior in a dog: keratotomy and extraction of a Cuterebra sp. larva. Vet Ophthalmol. 2014;17(6):448-53. PMID: 25186977.
20. Carastro S, Dugan S, Paul A. Intraocular dirofilariasis in dogs. Compend Contin Educ Pract Vet. 1992;14(2):209-17. https://www.cabidigitallibrary.org/doi/full/10.5555/19922267363
21. Goh YS, Kim HM, Alkathiri B, Chang HS, Yoon YM, Lee SH, et al. Two cases of ectopic dirofilariasis by Dirofilaria immitis in subconjunctival and subcutaneous tissues in dogs. Parasitol Int. 2023;92:102683. PMID: 36162804.
22. Dantas-Torres F, Lia RP, Barbuto M, Casiraghi M, Crovace A, Caligiani L, et al. Ocular dirofilariosis by Dirofilaria immitis in a dog: first case report from Europe. J Small Anim Pract. 2009;50(12):667-9. PMID: 19954444.
23. El Goulli AF, Zribi L, Sanhaji R, Chabchoub A, Bouratbine A, Gharbi M, et al. Study of ocular manifestations and humoral immune response in eyes of dogs with leishmaniasis. Vet Med Sci. 2023;9(2):625-37. PMID: 36253884; PMCID: PMC10029893.
24. Naranjo C, Fondevila D, Leiva M, Roura X, Peña T. Characterization of lacrimal gland lesions and possible pathogenic mechanisms of keratoconjunctivitis sicca in dogs with leishmaniosis. Vet Parasitol. 2005;133(1):37-47. PMID: 16023786.
25. Idrissi H, Hakkour M, Duchateau L, Zanatta R, Kachani M, Azrib R, et al. Canine leishmaniasis in morocco: a descriptive prospective clinical study. Vet Med Int. 2021;2021:6304127. PMID: 34531968; PMCID: PMC8440073.
26. Peña MT, Roura X, Davidson MG. Ocular and periocular manifestations of leishmaniasis in dogs: 105 Cases (1993-1998). Vet Ophthalmol.2000;3(1):35-41. https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1463-5224.2000.00106.x
27. Oriá AP, Pereira PM, Laus JL. Uveitis in dogs infected with Ehrlichia canis. Ciência Rural. 2004;34(4):1289-95. https://www.scielo.br/j/cr/a/jPwKw6dfVwLGt9fHbSgtpBz/
28. Komnenou AA, Mylonakis ME, Kouti V, Tendoma L, Leontides L, Skountzou E, et al. Ocular manifestations of natural canine monocytic ehrlichiosis (Ehrlichia canis): a retrospective study of 90 cases. Vet Ophthalmol. 2007;10(3):137-42. PMID: 17445073.
29. Little SE. Ehrlichiosis and anaplasmosis in dogs and cats. Vet Clin North Am Small Anim Pract. 2010;40(6):1121-40. PMID: 20933140.
30. Leiva M, Naranjo C, Peña MT. Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. Vet Ophthalmol. 2005;8(6):387-93. PMID: 16359361.
31. Johnson KL, Craig LE, Wilson S, McLarty E, Hespel AM. Radiographic evidence of metaphyseal sclerosis secondary to canine distemper virus: 4 cases in juvenile dogs. J Vet Intern Med. 2022;36(4):1303-11. PMID: 35656875; PMCID: PMC9308435.
32. Dik I, Hatipoglu D, Gulersoy E. Comparison of some cytokines, acute phase proteins and citrulline levels in healthy and canine distemper infected dogs. J Vet Med Sci. 2023;85(1):76-82. PMID: 36418074; PMCID: PMC9887225.
33. Willis AM. Canine viral infections. Vet Clin North Am Small Anim Pract. 2000;30(5):1119-33. PMID: 11033878.
34. Milke B, Carithers R. Chorioretinitis and detached retina as post-distemper lesions in the canine. Iowa State Univ Vet. 1975;37(2):40-3. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://dr.lib.iastate.edu/server/api/core/bitstreams/5b3cfbeb-07a3-47ef-a735-b12341234cd6/content
35. Richards TR, Whelan NC, Pinard CL, Alcala FC, Wolfe KC. Optic neuritis caused by canine distemper virus in a Jack Russell terrier. Can Vet J. 2011;52(4):398-402. PMID: 21731093; PMCID: PMC3058652.
36. de Almeida DE, Roveratti C, Brito FL, Godoy GS, Duque JC, Bechara GH, et al. Conjunctival effects of canine distemper virus-induced keratoconjunctivitis sicca. Vet Ophthalmol. 2009;12(4):211-5. PMID: 19604335.
37. Aroch I, Ofri R, Sutton GA. Slatter's Fundamentals of Veterinary Ophthalmology. In: David JM, Paul EM, Ron O. eds. Ocular Manifestations of Systemic Diseases. 4th ed. USA: Saunders; 2008. p.374-418.

38. Castro MDS, David MBM, Gonçalves EC, Siqueira AS, Virgulino RR, Aguiar DCF. First molecular detection of canine herpesvirus 1 (CaHV-1) in the Eastern Brazilian Amazon. J Vet Sci. 2022;23(2):e18. PMID: 35187876; PMCID: PMC8977539.
39. Decaro N, Martella V, Buonavoglia C. Canine adenoviruses and herpesvirus. Vet Clin North Am Small Anim Pract. 2008;38(4):799-814, viii. PMID: 18501279; PMCID: PMC7114865.
40. Ledbetter EC. Canine herpesvirus-1 ocular diseases of mature dogs. N Z Vet J. 2013;61(4):193-201. PMID: 23438442.
41. Ledbetter EC, Joslin AR, Spertus CB, Badanes Z, Mohammed HO. In vivo confocal microscopic features of naturally acquired canine herpesvirus-1 and feline herpesvirus-1 dendritic and punctate ulcerative keratitis. Am J Vet Res. 2021;82(11):903-11. PMID: 34669494.
42. Curtis R, Barnett KC. The ocular lesions of infectious canine hepatitis. 2. Field incidence. J Small Anim Pract. 1973;14(12):737-45. PMID: 4803914.
43. Wright NG. Canine adenovirus: its role in renal and ocular disease: a review. J Small Anim Pract. 1976;17(1):25-33. PMID: 175219.
44. Sykes JE. Infectious Canine Hepatitis. Canine and Feline Infectious Diseases. 2014:182–6. PMCID: PMC7151783.
45. Miller EJ, Brines CM. Canine diabetes mellitus associated ocular disease. Top Companion Anim Med. 2018;33(1):29-34. PMID: 29793726.
46. Holland CT. Bilateral Horner's syndrome in a dog with diabetes mellitus. Vet Rec. 2007;160(19):662-4. PMID: 17496275.
47. Wilkie DA, Gemensky-Metzler AJ, Colitz CM, Bras ID, Kuonen VJ, Norris KN, et al. Canine cataracts, diabetes mellitus and spontaneous lens capsule rupture: a retrospective study of 18 dogs. Vet Ophthalmol. 2006;9(5):328-34. PMID: 16939461.
48. Schechtmann SA, Stine JM, Miller TR, Welihozkiy A, Michau TM. A retrospective analysis of lipid-laden aqueous humor in dogs: Thirty cases. Vet Ophthalmol. 2020;23(2):277-85. PMID: 31733041.
49. Winiarczyk D, Winiarczyk M, Winiarczyk S, Michalak K, Adaszek Ł. Proteomic analysis of tear film obtained from diabetic dogs. Animals (Basel). 2020;10(12):2416. PMID: 33348610; PMCID: PMC7766195.
50. Gelatt K, Gilger B, Kern T. Veterinary ophthalmology. Ocular Manifestations of Systemic Disease. 5th ed. USA: Wiley-Blackwell; 2013. p.1949.
51. Plummer CE, Specht A, Gelatt KN. Ocular manifestations of endocrine disease. Compend Contin Educ Vet. 2007;29(12):733-43. PMID: 18225637.
52. MSD Manual Veterinary [Internet]. ©2023 Merck & Co., Inc. [Cited: November 6, 2023]. Treatment and prognosis for cushing disease in animals. Available from: https://www.msdvetmanual.com/endocrine-system/the-pituitary-gland/cushing-disease-pituitary-dependent-hyperadrenocorticism-in-animals#v3270741
53. Mooney CT. Canine hypothyroidism: a review of aetiology and diagnosis. N Z Vet J. 2011;59(3):105-14. PMID: 21541883.
54. Rezaei M, Saberi M, Shafiian A. Bilateral corneal lipidosis secondary to hypothyroidism in a terrier. Comp Clin Path. 2015;24(4):975-7. https://link.springer.com/article/10.1007/s00580-015-2083-2
55. Dixon RM, Reid SW, Mooney CT. Treatment and therapeutic monitoring of canine hypothyroidism. J Small Anim Pract. 2002;43(8):334-40. PMID: 12201441.
56. Cullen CL, Rose PL, Grahn BH. Diagnostic ophthalmology. Can Vet J. 2002;43(4):307-8. PMID: 11963669; PMCID: PMC339245.
57. Naranjo C, Schobert C, Dubielzig R. Canine ocular gliomas: a retrospective study. Vet Ophthalmol. 2008;11(6):356-62. PMID: 19046275.
58. Kenny PJ, Vernau KM, Puschner B, Maggs DJ. Retinopathy associated with ivermectin toxicosis in two dogs. J Am Vet Med Assoc. 2008;233(2):279-84. PMID: 18627233.
59. Mizukami K, Yabuki A, Endoh D, Chang HS, Lee KW, Nakayama M, et al. Investigation of parallel and simultaneous selection for collie eye anomaly and ivermectin toxicosis. Vet Rec. 2014;175(7):174. PMID: 24939474.
60. Epstein SE, Hollingsworth SR. Ivermectin-induced blindness treated with intravenous lipid therapy in a dog. J Vet Emerg Crit Care (San Antonio). 2013;23(1):58-62. PMID: 23317101.
61. Griggs AN, Allbaugh RA, Tofflemire KL, Ben-Shlomo G, Whitley D, Paulsen ME. Anticoagulant rodenticide toxicity in six dogs presenting for ocular disease. Vet Ophthalmol. 2016;19(1):73-80. PMID: 25800104.
62. Valchev I, Binev R, Yordanova V, Nıkolov Y. Anticoagulant rodenticide intoxication in animals- a review. Turkish J Vet Anim Sci. 2008;32(4):237-43. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://aj.tubitak.gov.tr/veterinary/issues/vet-08-32-4/vet-32-4-1-0607-12.pdf
63. Griggs AN, Allbaugh RA, Tofflemire KL, Ben-Shlomo G, Whitley D, Paulsen ME. Anticoagulant rodenticide toxicity in six dogs presenting for ocular disease. Vet Ophthalmol. 2016;19(1):73-80. PMID: 25800104.
64. Matthews BR, Lewis GT. Ehlers-Danlos syndrome in a dog. Can Vet J. 1990;31(5):389-90. PMID: 17423589; PMCID: PMC1480711.
65. Barnett KC, Cottrell BD. Ehlers-danlos syndrome in a dog: ocular, cutaneous and articular abnormalities. J Small Anim Pract. 1987;28(10):941-6. https://onlinelibrary.wiley.com/doi/10.1111/j.1748-5827.1987.tb01318.x
66. Estey CM. Congenital hydrocephalus. Vet Clin North Am Small Anim Pract. 2016;46(2):217-29. PMID: 26704658.
67. Katz ML, Narfström K, Johnson GS, O'Brien DP. Assessment of retinal function and characterization of lysosomal storage body accumulation in the retinas and brains of Tibetan Terriers with ceroid-lipofuscinosis. Am J Vet Res. 2005;66(1):67-76. PMID: 15691038.
68. Whiting REH, Robinson Kick G, Ota-Kuroki J, Lim S, Castaner LJ, Jensen CA, et al. Intravitreal enzyme replacement inhibits progression of retinal degeneration in canine CLN2 neuronal ceroid lipofuscinosis. Exp Eye Res. 2020;198:108135. PMID: 32634395; PMCID: PMC9261958.
69. Yamato O, Masuoka Y, Yonemura M, Hatakeyama A, Satoh H, Kobayashi A, et al. Clinical and clinico-pathologic characteristics of Shiba dogs with a deficiency of lysosomal acid beta-galactosidase: a canine model of human GM1 gangliosidosis. J Vet Med Sci. 2003;65(2):213-7. PMID: 12655116.
70. Hasegawa D, Yamato O, Nakamoto Y, Ozawa T, Yabuki A, Itamoto K, et al. Serial MRI features of canine GM1 gangliosidosis: a possible imaging biomarker for diagnosis and progression of the disease. ScientificWorldJournal. 2012;2012:250197. PMID: 22536126; PMCID: PMC3334264.