REVIEW ARTICLE
JIVA 18 (2) August 2020

Received: 26-06-2020
Accepted: 30-07-2020

OCULAR MANIFESTATIONS OF ENDOCRINE DISORDERS IN SMALL ANIMALS

Anoop S.[1*], Laiju M. Philip[2], Soumya Ramankutty[2], Sudheesh S. Nair[2] and John Martin K. D[3]

[1]Associate Professor, [2]Assistant Professor, [3] Professor and Head

Department of Veterinary Surgery and Radiology,
College of Veterinary and Animal Sciences, Mannuthy. Thrissur, Kerala-670651
**Corresponding author: anoop@kvasu.ac.in*

ABSTRACT

Endocrine diseases make up a significant percentage of the chronic diseases in small animal patients. Dogs and cats with endocrinopathies are at risk of developing many serious ocular signs that may jeopardize their quality of life. Most of the endocrinopathies including diabetes mellitus, Cushing's disease, growth hormone imbalance, hypothyroidism, hyperthyroidism etc. have ocular manifestations. A better understanding of such ocular manifestations will help in the early diagnosis of the disease condition as well as to undertake the prompt measures for prevention of their occurrence, slowing down the progress or treatment.

Keywords: Endocrinopathies, ocular manifestations, diabetes mellitus, hypothyroidism, hypocalcaemia.

INTRODUCTION

Endocrine system which produces specific hormones coordinate and control all the body activities. Many a times, disorders of the endocrine system are manifested in multi-organ fashion. Endocrinopathies, several of them, become apparent in the eye, first through a variety of distinct pathophysiologic disturbances. Thus, eye provides clinicians with valuable clues for the recognition and management of numerous endocrinopathies (Kamboj *et al.,* 2017). Timely recognition of these ophthalmic manifestations is critical not only for rapid diagnosis and treatment, but also to prevent significant morbidity and mortality in animals. The most common endocrinopathies having ocular manifestations seen in small animals are diabetes mellitus

(DM), hyperadrenocorticism (Cushing's disease), hypoadrenocorticism (Addison's diseases), growth hormone imbalances, hypothyroidism, hyperthyroidism and associated calcium imbalances.

1. Diabetes mellitus

Diabetes mellitus (DM) is the most common endocrine disorder in small animal patients, which may result in cataract formation, lens induced uveitis, endothelial cell loss and pleomorphism, reduced corneal sensitivity, hyperlipidemia, retinopathy, keratoconjunctival changes and other retinopathies (Gelatt, 1975). Secondarily it may even result in uveitis and poor corneal wound healing. Among humans, 47 to 67% of the diabetic patients also develop corneal lesions. Poodle, amidst the dog breeds, has a significantly excess risk than German shepherd, Cocker Spaniels, Collies and Boxers for the development of diabetes. It is significantly associated with cataract formation in both sexes (Marmor *et al.*, 1982). The most common ocular manifestations in dogs and cats with DM are discussed.

a. Cataract

Cataract is the earliest and most consistent ocular lesion in DM and studies suggest that majority of dogs with diabetes will develop cataract within 5-6 months and approximately 80% within 16 months of its diagnosis (Beam *et al.*, 1999). It is also observed that, all dogs with diabetes develop cataract at some point of its life time. Various factors like age, species, duration of diabetes and severity of hyperglycaemia also may affect the development of cataract. However young dogs are highly susceptible to the development of cataract in DM (Fig. 1). Cataract may occur in diabetic cats also but less frequently than in dogs and the reason may be attributed to the fact that aldose reductase activity is significantly lower in older cats than in dogs (Richter *et al.*, 2002). Aldose reductase is a rate limiting enzyme in the polyol pathway and is located in the eye (cornea, retina, lens), kidney, myelin sheath, and also in other tissues less involved in diabetic complications (Narayanan, 1993). Cataracts in DM initially develop as vacuoles at the equator of the lens and eventually occupy the entire lens. This necessitates pharmacological dilation of the pupil for early detection of diabetic cataract (Plummer *et al.*, 2007).

The avascular lens is freely permeable to glucose which is the main source of energy. By the process of diffusion, glucose enters the lens from the surrounding aqueous humor. Glucose is then converted to lactic acid via the anaerobic glycolytic pathway. Lactic acid then diffuses back out of the lens to enter circulation. However, when hyperglycemia

is persisting, there will be saturation of the hexokinase enzyme which is responsible for this conversion. Excess glucose then gets metabolised through the polyol pathway to sorbitol and fructose, which are not freely diffusible. In the presence of high glucose concentration, the enzyme aldose reductase which catalyses the reduction of glucose to sorbitol, not only has more substrate to act, but also it is up-regulated and thereby increasing its activity (Muirhead and Hothersall, 1995). The trapped sorbitol and fructose in the lens, act as hydrophilic osmotic agents and draw more water into the lens and causes welling and rupture of lens fibers, resulting in the lenticular opacities known as cataracts.

b. Lens induced uveitis

The strongly vascularized anterior uvea is used as a carrier and a connecting link to the immune system. DM induced cataract may lead to leakage of lens proteins and subsequently lead to uveitis. It will be charecterised by low IOP, miosis, aquous flare, corneal odema and even congestion (Woerdt *et al.,* 1992). Spontaneous cataract resorption and subsequent lens-induced uveitis are observed primarily in young dogs, especially in Afghan hound, American cocker spaniel, Boston terrier, miniature and toy poodle and miniature schnauzer. The resorption process, when extensive, may help to restore vision (Gelatt, 1975). However, the inflammatory response leading to a release of the lens material observed in domestic and laboratory animals exhibit only slight similarities with that in humans (Pfleghaar and Schaffer, 1992).

c. Corneal sensitivity

Diabetic dogs have significantly reduced corneal sensitivity in all the quadrants when compared with normal dogs. Regional variation in this corneal sensitivity is similar in both diabetic and non diabetic dogs. This impaired corneal sensitivity is due to the neuropathy of the ophthalmic division of trigeminal nerve which causes neurotropic keratopathy resulting in loss of sensory innervation to the cornea. Corneal nerve dysfunction and associated recurrent or non-healing ulcers were also reported in dogs (Kathryn *et al.,* 2003). In addition, the ocular surface disease in diabetes is characterized by a disorder of tear quantity and quality, squamous metaplasia, goblet cell loss and all of which seem to evolve in close proximity to the status of metabolic control and peripheral neuropathy (Dogru *et al.,* 2001). This diffuse neuropathy leading to reduced corneal sensitivity may subsequently lead to development of corneal ulcers. Corneal aesthesiometry can be used to measure the corneal sensitivity and corneal innervations. Reduced corneal

sensitivity is a classical feature in human diabetic patients too (Schultz *et al.,* 1981).

d. Hyperlipidemia

Hyperlipidemia is another common symptom in diabetic dogs and cats, especially if diabetes is not controlled. Hypertriglyceridemia occurs when there is relative or absolute insulin deficiency and associated decreased lipoprotein lipase activity. Hypercholesteremia may also occur due to its increased synthesis or impaired clearance (Feldman and Nelson, 2004). Hyperlipidemia may result in corneal lipid deposits, lipemia retinalis and lipemic aqueous humor. Lipemia retinalis is the presence of lipid-filled retinal vessels which appear yellow to orange in color and the contours of the retinal vessels will be readily visible during ophthalmoscopy (Fig. 2). Because of the color differences in the ocular fundus, lipemia retinalis is only visible in the non tapetal areas. The presence of a dark pigment behind the lipemic vessels enhances the color contrast and permits ready visualization of the lipemic vessels while the vessels overlying the tapetal retina appear normal (Aguiree and Gross, 1980). Like in humans, though infrequent, complications like atherosclerotic vascular diseases are reported in dogs and cats also (Hess *et al.*, 2002). Atherosclerosis, when associated with diabetes mellitus and hypothyroidism, may cause increased permeability of the uveal vessels and predisposes the animals to the development of lipemic uveitis (LU) (Sottiaux, 1999). Violette and Ledbetter (2019) in a study on etiologies of LU observed that the severity of LU may depend on the dog's natural predisposition to leak lipoproteins during uveitis as well as the severity of ocular or systemic disease.

e. Retinopathy

Diabetic retinopathy occurs when there is poor glycemic control and its diagnosis is often impossible due to early development of cataract which limits fundus examination (Engerman and Kern,1987). It is the most common ocular manifestation of DM and develops earlier in diabetic dogs. The pathogenesis of this disorder is most likely multifactorial metabolic alterations secondary to the hyperglycemic state, and micro vascular changes seen with diabetes (Munana, 1995). It results in development of retinal haemorrhages and micro aneurysms (RH-MA) which are considered as the markers of diabetic retinopathy in dogs. Retinopathy is a common finding in hypertensive cats with concurrent renal failure or hyperthyroidism and systemic hypertension. It is frequently seen in geriatric cats with ocular signs of bilateral intraocular hemorrhage, retinal edema and detachment, development of inner retinal ischemic spots ("cotton-

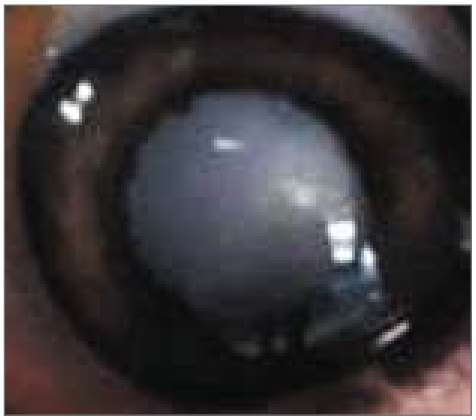

Fig. 1. Diabetic cataract

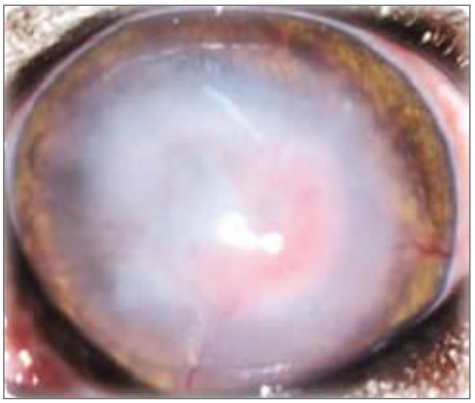

Fig. 3. Uveitis with mild vascularisation of cornea

wool") and vessel tortuosity, accompanied by localized or generalized narrowing of retinal arterioles (Boxtel, 2003). However diabetic retinopathy in animals is not that common as in humans (Landry *et al*., 2004).

f. Keratoconjunctival changes

DM may cause alterations in the precorneal tear film and development of dry eye or keratoconjunctivitis sicca (KCS). It is linked to poor metabolic control and peripheral neuropathy of lacrimal gland innervation. Acinar cells of the lacrimal

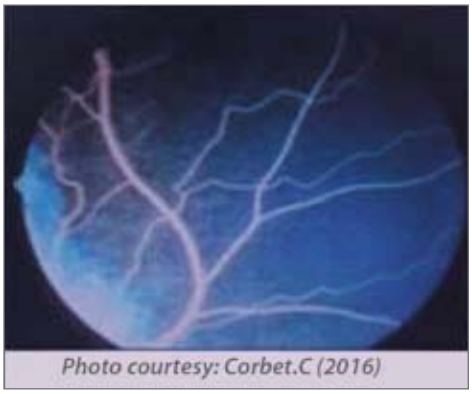

Fig. 2. Lipemia retinalis. Retinal vessels appear orange

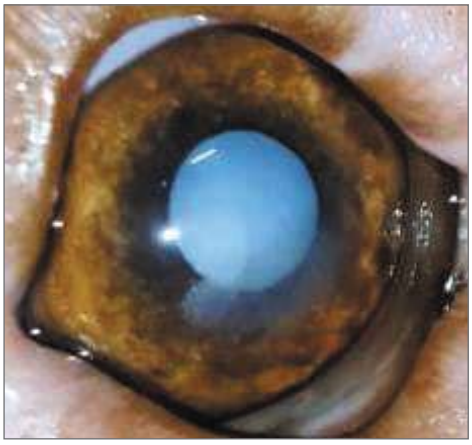

Fig. 4. Corneal lipid infiltration along with cataract.

Fig. 5. Horner's syndrome in the left eye. Note ptosis, miosis and third eyelid prolapse.

gland need insulin to stimulate its secretory component and its reduction may lead to decreased tear production. Schirmer tear test (STT) and mean tear film breakup time (TFBT) values which are indicative of basal tear production and quality of tear film respectively, will be lowered in DM patients (Cullen *et al*., 2005). Cheryl *et al*. (2005) also studied the effect of DM on tear production and observed that diabetic cataracteous dogs have significantly altered kertoconjunctival characteristics compared to non cataracteous and non diabetic non cataracteous dogs. KCS when occuring along with reduced corneal sensitivity makes the cornea prone for ulcer formation and subsequent complications.

2. Hyperadenocorticism (Cushing's disease)

Cushing's disease or hyper-adrenocorticism (HAC) often results in ophthalmic consequences due to excessive levels of corticosteroids. There will be subsequent development of retinal and corneal pathologies. Cushing's syndrome is common to some degree in majority of human patients taking long term corticosteroid therapy and ocular manifestations include raised intraocular pressure and exophthalmos (Chopra *et al*., 2012). Though common in dogs, HAC is very rare in cats. The most common ocular pathologies associated with HAC are hypertension induced changes, hyperlipidemia, immunosuppression, ectopic calcification, exophthalmos and sudden acquired retinal degeneration (SARD).

a. Hypertension induced changes

Retinal changes associated with systemic hypertension is due to increased hydrostatic pressure in choroid vasculature which may result in haemorrhage, non inflammatory swelling of the optic nerve head called papilledema, retinal detachment with sub retinal effusions and retinal degeneration. Haemorrhage that occurs may result in focal scarring of the fundus and death of the involved photoreceptors leading to formation of blind spots (Plummer *et al.,* 2007). Ocular hypertension may also cause hyphema and subsequent anterior or posterior uveitis (Fig. 3).

b. Hyperlipidemia

Primary hyperlipidemia has been reported in certain breeds of dogs like Miniature Schnauzers, Beagles, and Shetland Sheepdogs due to hereditary or familial lipoprotein dysregulation (Bauer, 1995 and Sato *et al.*, 2000). Whereas secondary hyperlipidemia has been reported as acquired due to an underlying disorder affecting lipid metabolism including DM, HAC, and hypothyroidism (Barrie

et al., 1993). Hyperlipidemia associated with HAC may result in lipemic aqueous humour and subsequent inflammation which may alter blood - aqueous barrier. Permeability of vessels increases which leads to the leakage of lipoproteins and results in turbidity of the aqueous humour which is called lipemic aqueous humour. When it occurs along with DM, there is additional risk of development of cataract and lens induced uveitis.

c. Immunosuppression

Excess cortisol in circulation may result in immunosuppression and may lead to development of endophthalmitis. When immune compromised, they are at risk for infection by a variety of pathogens targeting eye and may cause immune-mediated lesions of the posterior uvea and retina and occasionally the anterior uvea and cause endophthalmitis. In addition, excessive circulating cortisol places patients at risk for ectopic calcification and impaired vision (Plummer *et al.*, 2007).

d. Ectopic calcification

Increased osteoclastic activity due to HAC may lead to hypercalcemia and metastatic calcification. There will be calcium deposits in corneal stroma or superficial cornea leading to horizontal band of calcium crystals at palpebral fissure called band keratopathy leading to keratitis and corneal opacity (Ward, 1989). Laus *et al.* (2002) reported a case of bilateral corneal lipid and calcium degeneration in a 7-year-old female Poodle with HAC and observed that corneal degeneration may occur with a deposition of lipids or calcium, or both in hyperlipidemia associated with HAC.

e. Exophthalmos

Proptosis or exophthalmia is a common ocular manifestation of Cushing's disease. In addition, there will be facial nerve paralysis also. This exophthalmos and facial paralysis may result in exposure keratitis and subsequent corneal ulceration (Aterman and Greenberg, 1953).

f. Sudden acquired retinal degeneration (SARD)

It is a non-inflammatory retinal syndrome where there is degeneration and loss of photoreceptors cells in the retina. It is more common in female dogs above seven years of age. Though it is mostly associated with Cushing's syndrome, the exact mechanism is still unclear. Often, dogs with SARD are presented with acute, bilateral blindness and initially have normal results from a fundus examination (Komaromy *et al.*, 2016). Acute blindness from SARD has also been related to diseases of the pituitary-adrenal axis (Plummer *et al.*, 2007). It is a non-painful condition where there is gene induced apoptosis happening.

The condition should be differentiated from optic neuritis and tumours at the optic chiasm. Mattson *et al.* (1992) also reported that animals that are presented with SARD have systemic clinical signs consistent with those of Cushing's syndrome.

3. Hypoadrenocorticism (Addison's diseases)

Unlike Cushing's disease, hypoadrenocorticism (HOC) is very rare in dogs and cats and may not cause much ocular manifestations unless associated with other conditions like hypercalcemia. Naturally occurring HOC is an uncommon canine disease and young, female dogs are mostly affected. HOC, many a times results from immune-mediated destruction of adrenocortical layers, leading to deficiencies of mineralocorticoids and glucocorticoids (Klein and Peterson, 2010). It is common in humans and the ocular manifestations include ptosis, blepharitis, blepharospasm, keratoconjunctivitis with extreme photophobia, corneal ulcers, episcleritis, cataract and papilloedema (Langston, 2008).

4. Growth Hormone disorders

Growth hormone related issues are very rare in dogs but common in cats. Over secretion of growth hormone is seen connected with adenomas of the pars distalis of the pituitary gland whereas in dogs, it is reported to be associated with prolonged progesterone treatment (Eigenmann and Haagen, 1981). Deficiency of growth hormones and subsequent pituitary dwarfism is ubiquitous in German shepherd dogs. But Fracassi *et al.* (2014) observed acromegaly from over production of growth hormones in German shepherd dogs and exophthalmos as its ocular manifestation. Other common ophthalmic manifestations are papilledema, systemic hypertension, signs secondary to DM and blindness. Deficiency of growth hormone may result in lower levels of thyroid stimulating hormone and secondary hypothyroidism. The ocular manifestations will be subsequent to hypothyroidism. Blindness in cats subsequent to adenomas of the pituitary gland depends on the size and stage of the tumour.

5. Hypothyroidism

Hypothyroidism is another common endocrinopathy in dogs though rare in cats. Ocular signs are rare unless associated with hyperlipidemia or hyperlipoproteinemia. Corneal lipid deposits and infiltrates or lipid-laden aqueous humour and associated uveitis are the most common ocular manifestation of hypothyroidism (Fig. 4). Arcus lipoides corneae is common in hypothyroid German shepherd dogs and it appears as an opaque ring of crystalline lipid deposits along and within the

peripheral cornea near the limbus (Crispin, 1988). Hypothyroidism may result in some neurological changes also due to segmental demyelination and axonopathy. The most common neuropathy associated with hypothyroidism is facial nerve paralysis and Horner's syndrome (Fig. 6) (Kern *et al.,* 1989).

6. Hyperthyroidism

Though very rare in dogs, hyperthyroidism is seen very often common in old cats and is mostly associated with systemic hypertension. In dogs, malignant neoplasm of the thyroid may cause hyperthyroidism. There is a paucity of data regarding ocular signs of hyperthyroidism in dogs. The ocular manifestations of hyperthyroidism in cats are associated with hypertension which may even go above 160 mm of Hg (Stiles *et al.,* 1994). There will be acute loss of vision and the other ocular changes are retinopathy with detachments, sub-retinal effusion and haemorrhage and hyphema (Maggio *et al*., 2000).

7. Calcium disorders

Calcium disorders are very frequently associated with the endocrinopathies.

a. Hypocalcaemia

Hypocalcaemia can be caused by a number of conditions, including primary hypoparathyroidism, renal failure, pancreatitis, eclampsia and C-cell tumours that result in excess secretion of calcitonin (Delmere and Paterson, 1981). The characteristic ocular manifestation with hypocalcaemia is cataract formation with classic multifocal bilateral opaque appearance in the lens (Bassett, 1998). The main mechanism of the development of cataract is due to the imbalance with the active cation transport mechanism which may bring about osmotic imbalance and subsequent rupture of lens fibres leading to cataract formation. (Evans and Kern, 1931).

b. Hypercalcemia

When an animal's serum calcium concentration exceeds established normal levels, hypercalcemia occurs and the possible reasons could be primary hyperparathyroidism, hypercalcemia of malignancy, HOC, vitamin D toxicity, osteoclastic diseases, granulomatous diseases, renal failure, or hyperthyroidism (Feldman and Nelson, 2004). When there is hypercalcemia there will be metastatic calcification and development of band keratopathy. There can be even deposits in conjunctiva and other ocular and orbital tissues, in addition to more traditional locations, such as the skin, lungs, or renal pelvises (Aurbach, 1985).

However, it is also important to consider contributing problems, such as renal failure and hyperthyroidism which may not be directly attributable to the elevated calcium concentration but may result in ocular abnormalities.

CONCLUSION

Several of the endocrinopathies in animals have ocular manifestations and when ophthalmic disease is directly or indirectly caused by an endocrine disorder, treatment of the ocular signs is invariably aimed at or facilitated by treatment or control of the underlying cause. It is essential for the practicing veterinarians to be aware of the potential ocular consequences of endocrinopathies so that potentially painful or vision-threatening problems can be addressed early, thereby preventing more serious complications.

REFERENCES

Aguiree, G.D and Gross, S.L. 1980. Ocular manifestation of selected Systemic Diseases. *Compendium on Continuing Education for the Practicing Veterinarian.* **2**(2): 144-153.

Aterman, K and Greenberg, S.M. 1953. Experimental exophthalmos in rats produced by cortisone. *Endocrinology*. **52**(5): 510–517

Aurbach, G.D. 1985. Parathyroid hormone, calcitonin and the calciferols, in Wilson JD, Foster DW (eds): Williams Textbook of Endocrinology, Ed 7. WB Saunders. Philadelphia, 1137p.

Barrie, J., Watson, T., Stear, M. and Nash, A.S. 1993. Plasma cholesterol and lipoprotein concentrations in the dog: the effects *of* age, breed, gender and endocrine disease. *J. Small Anim. Pract.* **34**: 507-512.

Bassett, J.R. 1998. Hypocalcemia and hyperphosphatemia due to primary hypoparathyroidism in a six-month-old kitten. *J. Am. Anim. Hosp. Assoc.* **34** (6): 503-507.

Bauer, J.E. 1995. Evaluation and dietary considerations in idiopathic hyperlipidemia in dogs. *J. Am. Vet. Med. Assoc.* **206**: 1684-1688.

Beam, S., Correa, M.T. and Davidson, M.G. 1999. A retrospective cohort study on the development of cataracts in dogs with diabetes mellitus: 200 cases. *Vet. Ophthalmol*. **2**: 169-172.

Boxtel, S.A.V. 2003. Hypertensive retinopathy in a cat. *Can.Vet. J.* **47** (2): 147-149.

Cheryl, L., Cullen, H., Sherri, L., Aubery, A., Webb, A.A. and Carole, M.C. 2005. Keratoconjunctival effects

of diabetes mellitus in dogs. *Vet. Ophthalmol*. **4**: 215-224.

Chopra, R., Chander, A. and Jacob, J.J. 2012. The eye as a window to rare endocrine disorders. *Ind. J. Endocrinol. Metab*. **16**(3): 331-338.

Crispin, S.M. 1988. Crystalline corneal dystrophy in the dog: Histochemical and ultrastructural study. *Cornea*. **7**: 149–161.

Cullen, C.L., Ihle, S.L., Webb, A.A. and Mc-Carville, C. 2005. Keratoconjunctival effects of diabetes mellitus in dogs. *Vet. Ophthalmol*. **8** (4): 215-224.

Delmere, N. and Paterson, C. 1981. Hypocalcemic Cataract. In: Mechanism of Cataract formation in Human Lens. Duncan (ed), Academic Press, London: 219-236

Dogru, M., Katakami, C. and Inoue, M. 2001. Tear function and ocular surface changes in non-insulin dependent diabetes mellitus. *Ophthalmol*. **108**: 586–592.

Eigenmann, J.E. and Venker-van Haagen, A.J. 1981. Progestagen-induced and spontaneous canine acromegaly due to reversible growth hormone overproduction. Clinical picture and pathogenesis. *J. Am. Anim. Hosp. Assoc*. **17**: 813-822.

Engerman, R.L. and Kern, T.S. 1987. Progression of incipient diabetic retinopathy during good glycemic control. *Diabetes.* **36**: 808.

Evans, E. and Kern, R. 1931. The relation of the parathyroid gland to cataract. *Am. J. Ophthalmol.* **14**: 1029-1036.

Feldman, E.C and Nelson, R.W. 2004. Canine diabetes mellitus. In: Canine and Feline Endocrinology and Reproduction, Ed 3. WB Saunders. St. Louis, pp 486–538.

Fracassi, F., Zagnoli, L., Rosenberg, D., Furnanello, T. and Caldin, M. 2014. Spontanious acromegaly- A retrospective case control study in German shepherd dogs. *The Vet. J.* **202**: 69-75

Gelatt, K.N. 1975. Spontaneous cataract resorption and lens-induced uveitis in the dog. *Mod. Vet. Pract*. **56**(5): 331-335.

Hess, R.S., Kass, P.H and Winkle, T.J. 2002. Association between hypothyroidism, diabetes mellitus and hyperadrenocorticism and the development of atherosclerosis in dogs [abstract]. *J. Vet. Intern. Med.* **16**: 360.

Kamboj, A., Lause, M. and Kumar, P. 2017. Ophthalmic manifestations of

endocrine disorders- endocrinology and the eye. *Translational Paediatrics.* **6**(4): 286-299.

Kathryn, L., Good, M., Maggs, D., Hollingsworth, S., Scaglietti, R and Nelson, R. 2003. Corneal sensitivity in dogs with diabetes mellitus. *Am. J. Vet. Res*. **64**(1): 7-11.

Kern, T.J., Aromando, M.C. and Erb, H.N. 1989. Horner's syndrome in dogs and cats: 100 cases (1975–1985). *J. Am. Vet. Med. Assoc*. **195**: 369-373.

Klein, S.C and Peterson, M.E. 2010. Canine hypoadrenocorticism: Part 1. *Can. Vet. J.* **15**(1): 63-69.

Komaromy, A.M., Abrams, K.L., Heckenlively, J.R., Lundy, S.K., Maggs, D.J., Leeth, C.M., MohanKumar, P.S., Jones, S.M.P., Serreze, D.V and Woerdt, A.V. 2016. Sudden acquired retinal degeneration syndrome (SARDS) – a review and proposed strategies toward a better understanding of pathogenesis, early diagnosis and therapy. *Vet. Ophthalmol*. **19**(4): 319-331.

Landry, M.P., Herring, I.P and Panciera, D.L. 2004. Funduscopic findings following cataract extraction by means of phaecoemulsification in diabetic dogs: 52 cases (1993–2003). *J. Am. Vet. Med. Assoc*. **225**: 709–716.

Langston, D.P. 2008. Manual of ocular diagnosis and therapy. 6th Ed. Lippincott Williams and Wilkins. Philadelphia: Ocular manifestations of systemic disease, p. 444.

Laus, J.L., Santos, C.D., Talieri, I.C., Oriá. A.P and Bechara, G.H. 2002. Combined corneal lipid and calcium degeneration in a dog with hyperadrenocorticism: a case report. *Vet. Ophthalmol*. **5(**1): 61-63.

Maggio, F., DeFrancesco, T.C and Atkins, C.E. 2000. Ocular lesions associated with systemic hypertension in cats: 69 cases (1985–1998). *J. Am. Vet. Med. Assoc.* **217**(5): 695-702.

Marmor, M., Willeberg, P. and Glickman, L.T. 1982. Epizootiologic patterns of diabetes mellitus in dogs. *Am. J. Vet. Res.* **43**:465–470.

Mattson, A., Robersts, S.M and Isherwood, I.M. 1992. Clinical features suggesting hyperadrenocorticism associated with sudden acquired retinal degeneration. *J. Am. Anim. Hosp. Assoc.* **28**: 199-202.

Muirhead, R.P and Hothersall. J.S. 1995. The effect of phenazine methosulphate

on intermediary pathways of glucose metabolism in the lens at different glycaemic levels. *Exp. Eye Res*. **61**: 619-621.

Munana, K.R. 1995. Long-term complications of diabetes mellitus, Part I: Retinopathy, nephropathy, neuropathy. *Vet. Clin. North Am. Small Anim. Pract.* **25**(3): 715-730.

Narayanan. S. 1993. Aldose reductase and its inhibition in the control of diabetic complications. *Ann. Clin. Lab. Sci*. **23**(2): 148-158.

Pfleghaar, S and Schäffer, E.H. 1992. Lens-induced uveitis (endophthalmitis phako anaphylactica) in domestic animals. *Tierarztliche Praxis.* **20**(1): 7-18.

Plummer, C.E., Specht, A. and Gelatt, K.N. 2007. Ocular manifestations of endocrine diseases. *Compend. Contin. Educ. Vet.* **29**(12): 733-743.

Richter, M., Guscetti, F. and Spiess, B. 2002. Aldose reductase activity and glucose related opacities in incubated lenses from dogs and cats. *Am. J. Vet. Res.* **63**(11): 1591-1597.

Sato, K., Agoh, H. and Kaneshige T. 2000. Hypercholesterolemia in Shetland sheepdogs. *J. Vet. Med. Sci*. **62**: 1297-1301.

Schultz, R.O., Horn, D.L and Peters, M.A. 1981. Diabetic keratopathy. *Trans. Am. Ophthalmol. Soc*. **79**: 180–199.

Sottiaux, J. 1999. Atherosclerosis in a dog with diabetes mellitus. *J. Small Anim. Pract.* **40**: 581-584.

Stiles, J., Polzin, D.J and Bistner, S.I. 1994. The prevalence of retinopathy in cats with systemic hypertension and chronic renal failure or hyperthyroidism. *J. Am. Anim. Hosp. Assoc*. **30:** 564-572.

Violette, N.P and Ledbetter E.C. 2019. Lipemic uveitis and its etiologies in dogs: 75 cases. *Vet. Ophthalmol.* **22**: 577–583.

Ward, D.A. 1989. B and keratopathy associated with hyperadrenocorticism in the dog. *J. Am. Anim. Hosp. Assoc.* **25**: 583-586.

Woerdt, V.A., Nasisse, M. P and Davidson, M.G. 1992. Lens-induced uveitis in dogs: 151 cases (1985–1990). *J. Am. Vet. Med. Assoc.* **201**: 921-926.