



PROCEEDINGS

Winter Meeting

Birmingham Metropole, UK

Friday 11th to Sunday 13th November 2005



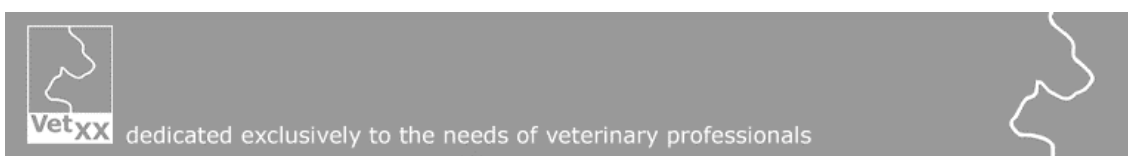
Contents

The Anterior Segment	1
Programme	2
Glaucoma - current concepts in pathophysiology (<i>G McLellan</i>)	3
Feline glaucoma (<i>G McLellan</i>)	10
What's new in the management of glaucoma? (<i>G McLellan</i>)	13
Diagnosis and Management of Equine Ocular SCC (<i>D Knottenbelt, Liverpool</i>)	19
Diagnosis and Management of Equine Ocular Sarcoids (<i>D Knottenbelt, Liverpool</i>)	22
Gill's ophthalmic tips (<i>G McLellan</i>)	26
Nutrition and the eye (<i>G McLellan</i>)	28
What's new in Equine Uveitis (<i>G McLellan</i>)	35
A Series of Qualitative Tear Deficiency Cases in Beagles (<i>H Ehall</i>)	39
Ocular penetration associated with dental extraction in the cat: 6 eyes (<i>JM Mould & FM Billson</i>)	41
Mast Cell Tumour of the Nictitans Conjunctiva Presenting As An Intermittent Exophthalmos (<i>KM Smith & S Murphy</i>)	43
Myopia in three dogs associated with early compromise in visual experience. (<i>DL Williams</i>)	47
The Retrobulbar Space	49
Our Sponsors!	53

The Anterior Segment

Autumn rolls around again, season of mists, mellow fruitfulness and the BrAVO meeting! And if you've missed coming to these meetings before, let me tell you that the opportunity to catch up with others interested in the field is always mellow and the programme laid on for us with regard to lectures is always fruitful! Enough of my driveling! The only thing I'd say is how disappointed I am to see only three abstracts presented – I'm sure there are many more of you out there in general practice with plenty of fascinating cases and a huge amount of potential clinical research material who could share it with the rest of us – its not that scary – honest!

David Williams



Programme

Saturday

- 8.00 – 9.30 Registration
- 9.30 – 10.15 Glaucoma - current concepts in pathophysiology (*G Mclellan*)
- 10.15 – 10.45 Feline glaucoma (*G Mclellan*)
- 10.45 – 11.15 Coffee and commercial exhibition
- 11.15 – 11.45 What's new in the management of glaucoma? (*G Mclellan*)
- 11.45 – 12.30 Diagnosis and Management of Equine Ocular SCC (*D Knottenbelt, Liverpool*)
- 12.30 – 14.00 Lunch and commercial exhibition
- 14.00 – 15.00 Diagnosis and Management of Equine Ocular Sarcoids (*D Knottenbelt, Liverpool*)
- 15.00 – 15.30 Gill's ophthalmic tips (*G Mclellan*)
- 15.30 – 16.00 Coffee and commercial exhibition
- 16.00 – 17.00 Abstracts 16.00 – 16.15 H Ehall
16.15 – 16.30 JM Mould and FM Billson
16.30 - 16.45 KM Smith and S Murphy
16.45 – 17.00 DL Williams
- 17.00 – 18.00 Tales of the unexpected (*Panel*)
- 18.00 Finish

Sunday

- 9.00 – 9.45 What's new in cataract surgery (*D Gartry, Moorfields Eye Hospital, London*)
- 9.45 – 10.30 Lasik eye surgery (*D Gartry, Moorfields Eye Hospital, London*)
- 10.30 – 11.30 Coffee and commercial exhibition
- 11.30 – 12.00 Letter from America (*G.Mclellan*)
- 12.00 - 14.00 Lunch
- 14.00 – 14.45 Nutrition and the eye (*G.Mclellan*)
- 14.45 – 15.30 What's new in Equine Uveitis *G.Mclellan*)
- 15.30 Finish

Glaucoma – Current Concepts in Pathophysiology
Gill McLellan B.V.M.S., Ph.D., D.V.Ophthalm., DipECVO
Assistant Professor, Veterinary Clinical Sciences
Iowa State University, Ames, Iowa 50011, USA

Intraocular Pressure- the usual suspect

In veterinary patients, the single most consistent feature of all glaucomas characterized to date is elevation in intraocular pressure (IOP). Intraocular pressures > 25mmHg in dogs and > 31mmHg in cats, or differences of more than a few mmHg between eyes should be considered suspicious. However, many factors can influence IOP measurements – including breed, age and gender, method of restraint, time of day, the technique of the “tonometrist” and the tonometer itself. Hence, it is very difficult to provide a precise “cut-off” point for determining normal versus abnormal IOP. For this reason, one should always interpret tonometry readings in light of other clinical findings.

“Let it flow” – aqueous humor in equilibrium

Maintenance of a physiologic IOP relies on a delicate equilibrium between aqueous humour production and outflow. Aqueous is produced by the ciliary processes, by a combination of mechanisms including diffusion, ultrafiltration and active secretion, into the posterior chamber. From the posterior chamber, aqueous flows through the pupil into the anterior chamber, then enters the ciliary cleft via spaces within the pectinate ligament, which spans the iridocorneal angle (ICA). Within the ciliary cleft, aqueous humour percolates through spaces between collagenous beams of the uveal trabecular meshwork (TM), then corneo-scleral TM. The corneoscleral TM is closely associated with the collector vessels of the angular aqueous plexus, which are analogous to the annular “Schlemm’s canal” of primates.^[1] Fluid is then transported by a pressure dependent mechanism, via the vacuolating endothelium of the angular aqueous plexus, to the radially oriented collector channels of the intrascleral venous plexus. From there, aqueous passes into the scleral and choroidal veins.

Intraocular pressure can be broadly defined by a relatively simple equation.

Goldmann Equation: $P_o = (F / C) + P_e$ where

P_o = IOP in mmHg P_e = episcleral venous pressure in mmHg

F = rate of aqueous formation in $\mu\text{l} / \text{min}$ and C = facility of aqueous outflow in $\mu\text{l} / \text{min} / \text{mmHg}$

In addition to pressure dependent “conventional” drainage via the trabecular meshwork into intrascleral and episcleral veins, aqueous can also percolate via a posterior “uveoscleral” route through the ciliary body interstitium to the suprachoroidal space and vortex veins. Uveoscleral outflow has been estimated to account for about 3% of aqueous outflow in normal cats, and about 15% of aqueous outflow in normal dogs.^[2, 3]

Mechanisms for IOP elevation:

To date, no instances of IOP elevation related to increased aqueous humour formation have been documented in veterinary glaucoma patients. The key mechanisms for IOP elevation are therefore reduction in the facility for aqueous outflow and/or increase in episcleral venous pressure.^[4-6]

Increase in episcleral venous pressure occurs, for example, in animals with orbital space occupying lesions, or as a result of inappropriate restraint restricting jugular blood flow, including tight collars.^[7] Reduction in the facility of aqueous outflow may be a primary abnormality or, as is frequently the case in veterinary patients, may be secondary to other ocular or systemic disease processes such as cataract, uveitis, lens luxation, neoplasia, retinal detachment and haemorrhage.^[4-6, 8, 9]

Where’s the block? Pupil, angle, cleft or beyond?

Pupil block:

Arguably the easiest mechanism of aqueous outflow obstruction for us to understand is the concept of “pupil block”. Anterior lens luxation, anterior vitreous prolapse, intumescent cataract and extensive posterior synechiae are all relatively common causes of pupil block glaucoma. Flow of aqueous humour from the posterior chamber to the anterior chamber is obstructed at the level of pupil and is therefore unable to exit through the conventional outflow pathways via the iridocorneal angle and ciliary cleft. Elevation in pressure within the posterior chamber leads to forward displacement of the iris, collapse of the ciliary cleft, narrowing of the iridocorneal angle and a shallow anterior chamber. The anterior chamber may be diffusely shallow, or may vary in depth as in iris bombé.

“Open-Angle, Closed-Angle”

Traditionally, clinically veterinary ophthalmologists have tended to classify glaucomas on the basis of gonioscopic findings as either “open angle” or “closed angle”. In reality, what we are really referring to is not simply the irido-corneal angle (ICA), but the opening to the ciliary cleft. In contrast, veterinary pathologists have tended to classify many of the primary glaucomas as “open-angle, closed-cleft”.^[8] This has led to confusing discrepancies in the clinical and histopathological classification of the canine and feline glaucomas.

Until very recently our ability to visualize and clinically characterize the ciliary cleft *in vivo* was extremely limited. Refined imaging techniques, such as Ultrasound Biomicroscopy (UBM), with probe frequencies around 50MHz, and High Resolution Ultrasonography (HRUS), with probe frequencies around 20MHz, offer us a greater appreciation for the dynamic changes that take place within the aqueous outflow pathways in our glaucomatous patients.^[10-14] These new technologies should facilitate the harmonization of clinical and pathological classification schemes as well as improve our insight into the pathogenic mechanisms involved in each individual patient.

Mechanisms for Angle Closure

Secondary angle closure glaucoma may occur as a sequela of pupil block, as the iris is “pushed forward”, occluding the opening of the iridocorneal angle. Multiple iridociliary cysts, as sporadically encountered in the Golden Retriever and Great Dane breeds, may also lead to anterior displacement of the ciliary zone of the iris contributing to secondary angle closure.^[15, 16] Theoretically, in such cases, it should be possible to “open” the angle during indentation gonioscopy, but as the ciliary cleft collapses, angle closure can become permanent. Alternatively, the iris may be “pulled forward”, as occurs in association with contracture of pre-iridal fibrovascular membranes (PIFVM), in a mechanism that can ultimately lead to extensive peripheral anterior synechiae. Obstruction of the trabecular meshwork and/or obliteration of the ciliary cleft by cellular infiltrates or debris may lead to the development of glaucoma secondary to neoplasia, uveitis and intraocular hemorrhage.^[6, 8, 9, 17] Obstruction at the level of the ICA and ciliary cleft also occurs in dogs with primary ocular melanosis, or so-called pigmentary glaucoma, that has been most extensively studied in the Cairn terrier breed.^[18-20]

Pectinate Ligament Dysplasia as a risk factor

Until advanced imaging modalities such as UBM and HRUS become more accessible, gonioscopy will remain the only, albeit flawed, means of evaluating the aqueous outflow pathway available to most veterinary ophthalmologists. Unfortunately, gonioscopy is a tricky and subjective diagnostic technique and requires considerable practice to achieve consistency in interpretation of gonioscopic features. The pectinate ligament and the width of the ICA should both be evaluated, bearing in mind that the width of the ICA can vary considerably throughout its circumference. The ratio of the width of the pectinate ligaments relative to the distance between the pectinate ligament origin and the cornea (just anterior to the superficial pigment zone) should be estimated. One classification scheme, proposed by Ekesten, defined the ICA of Samoyeds as “closed” if the ratio was ≤ 0.15 , “narrow” if 0.15-0.3, “slightly narrow” if 0.3-0.45, “open” if 0.45-0.55, and “wide open” if the ratio was > 0.55 . In the same study, PLD was diagnosed if abnormalities were noted over $> 1/16$ of the circumference of the ICA.^[21] Other investigators graded PLD on the basis of percentage of the ICA circumference affected on gonioscopy, and documented glaucoma only in dogs with severe grades of PLD and angle narrowing.^[22, 23]

A number of studies have clearly demonstrated that there is a link between degree of PLD and the development of glaucoma, and that predisposition to glaucoma is a heritable trait.^[23-26] In studies involving Flat Coated retrievers, Great Danes and English Springer spaniels, overt glaucoma was only documented in those animals with the most severe gonioscopic abnormalities and the degree of PLD had a heritable basis.^[22-25] Although gonioscopy may reveal pectinate ligament dysplasia (PLD) in a significant number of dogs within certain breeds, we now know that only a few of these animals actually go on to develop glaucoma.^[5, 21, 23-29] Experimental disruption of the pectinate ligament can increase perfusion rates in canine eyes *in vitro*, but it is clearly not the most important source of resistance to aqueous outflow.^[30] However, PLD may signal the existence of other developmental abnormalities within the structures of the ciliary cleft.^[27] The limitation of gonioscopy in our clinical evaluation of the canine aqueous outflow pathway was recently highlighted by histopathological identification of pectinate ligament dysplasia and ciliary cleft collapse in Norwegian elkhounds, a breed previously classified as affected by a chronic, slowly progressive, “open-angle” glaucoma.^[31, 32] Histopathological studies, however, are also associated with important limitations, including the obvious tendency to examine only globes obtained at a late stage in the disease process.

In humans, the term “goniodysgenetic glaucoma” applied to infants that have developmental malformations of the “anterior chamber angle”, which in humans is the location of the TM. These angle abnormalities lead to congenital or paediatric glaucoma. However, in dogs the mechanism for IOP elevation in association with so-called “goniodysgenesis” is complex, with many factors contributing to IOP elevation that characteristically is not manifest until much later in life.^[28] Severe PLD, narrow ICA, relatively anterior lens position, thick lens, and shallow anterior chamber, may all be considered as anatomic risk factors, i.e. markers indicating predisposition to glaucoma.^[25, 33] Similar anatomic risk factors may predispose human and canine subjects to primary angle closure glaucoma. However, only a small proportion of individuals with these characteristic risk factors go on and develop glaucoma. Elucidating the mechanisms that precipitate acute IOP elevations in these dogs will greatly enhance our ability to treat, and hopefully prevent or delay the onset of, glaucoma in “at-risk” eyes.

From “at risk” to acute glaucoma – pathogenic mechanisms

In dogs with PACG, proposed mechanisms for glaucomatous crises include both morphologic changes leading to progressive narrowing of the iridocorneal angle with age,^[34] and the development of acute pupil block.^[13] Acute pupil block is a dynamic process that, contrary to popular belief, doesn’t occur when the pupil is either intensely miotic or dilated, but when the pupil is relatively small to mid-range. It has been proposed that a very small segment of the iris, right at the pupil margin, is held in apposition against the anterior lens capsule by a complex dynamic mechanism that involves “iris stretch” and combined “blocking forces” generated by both the sphincter and dilator muscles.^[35, 36] In humans, transient episodes of pupil block may be interrupted by bright sunlight or sleep. Age-related changes in morphologic features such as lens thickness may, at least in part, contribute to angle closure and the development of glaucoma in middle-aged and older dogs.^[33] Studies utilizing HRUS identified a “floppy” iris conformation, likely to predispose to both lens-touch, and also angle narrowing on pupil dilation, in “at-risk” canine eyes.^[14] In dogs with acute PACG, HRUS demonstrated a sigmoid iris conformation, pupil block and ciliary cleft collapse.^[13] Recent histopathological studies have identified dispersion of pigment from the posterior iris epithelium, supporting the role played by “iris touch”, i.e. iris-lens contact, in the pathogenesis of glaucoma in dogs with primary goniodysgenesis-related glaucoma.^[37] Significant uveal inflammation was also identified in canine eyes with acute glaucoma. Whether uveitis plays a role in precipitating episodes of glaucoma due to iris thickening or miosis, or whether inflammation is a secondary phenomenon in dogs with primary glaucoma remains unclear.^[37] There is a suspicion that in many affected dogs, transient episodes of pupil block, with subsequent spontaneous resolution, precede confirmed glaucomatous crises. Microarray analysis has revealed abnormalities in gene expression in the “at risk eye” of a dog with confirmed primary glaucoma, which may either reflect undiagnosed episodes of previous IOP elevation or could offer clues as to the pathogenesis of disease.^[38]

Open-angle glaucoma

In humans, primary open-angle glaucoma (POAG) is an important cause of blindness, and is responsible for vision loss in millions of people worldwide. In contrast, POAG is encountered infrequently in veterinary patients. Although uncommonly encountered in practice, heritable POAG has been extensively studied in dogs, due to the establishment of a colony of affected Beagles at the University of Florida by Dr Kirk Gelatt and his co-workers.^[39] Abnormalities in ocular vascular resistance, tonographic aqueous outflow facility (which progressively declines from several months of age) and IOP have been confirmed in affected dogs, prior to the late-stage development of angle closure and advanced glaucoma that occurs from about the third year of life.^[5, 39-41]

In Beagles, as in humans with POAG, the precise mechanism for aqueous outflow obstruction remains unclear. However, the site of increased aqueous outflow resistance in POAG appears to reside in the trabecular meshwork and its extracellular matrix. In addition to the accumulation of abnormal, enzyme resistant glycosaminoglycans in the extracellular meshwork of the TM of affected dogs, abnormal amounts of myocilin protein have been identified in eyes of affected Beagles.^[42-44] A myocilin gene mutation was the first of the “glaucoma genes” to be identified in human POAG patients.^[45] Myocilin was formerly known as the Trabecular-meshwork Inducible Glucocorticoid Response (TIGR) gene and influences the likelihood of an individual to respond to topical corticosteroid therapy with an elevation in IOP.^[46] Although steroid-induced glaucoma does not appear to be a significant clinical concern in cats and dogs, elevation in IOP has been documented in cats and dogs treated topically with corticosteroids.^[47-49] We have recently excluded mutation in the myocilin gene in Siamese cats with primary glaucoma. However, investigations in glaucomatous cats and particularly in Beagles with POAG, may still offer clues as to this protein’s role in the development of POAG and steroid-induced glaucoma in humans.

Mechanisms for ganglion & photoreceptor cell death

In glaucomatous optic neuropathy, there is a loss of large diameter optic nerve axons^[6, 50, 51] An important mechanism of ganglion cell death and axon degeneration in glaucomatous optic neuropathy is interruption in the supply of neurotrophic factors from the CNS. Axonal transport interruption has been shown to occur at the level of the lamina cribrosa in response to elevated intraocular pressure in many species, including dogs and cats.^[51-53]

In acute congestive canine glaucoma, where IOP is frequently >50mmHg, there is evidence to support an important role for ischaemia in cell death within both the inner and outer retina.^[54-56] Proposed mechanisms responsible for initiation of cell death, by both necrosis and apoptosis, include glutamate release and resulting excitotoxicity, taurine depletion, increased nitric oxide synthesis, as well as lack of neurotrophic factors. Severe damage to the inner and outer retina and optic nerve can be observed in dogs at a very acute stage of disease.

The Bottom Line - glaucoma is a neurodegenerative disease

Glaucoma should not be regarded as a single entity, but should be considered to represent a large, diverse group of disorders that all result in optic nerve and retinal pathology and ultimately loss of vision.

Genetics and genomics : the light at the end of the tunnel?

The pathogenesis of glaucoma is multifactorial, and inherited predisposition to development of canine PACG is likely a complex trait. However, significant genetic and clinical evidence is now available to inform breeding strategies, in order to reduce the incidence of this painful and disabling disease.^[57] At present, the best that we can do is to assist in the formulation of selective breeding policies, by identifying genetically predisposed individuals based on phenotype. Ongoing advances in comparative genomics and proteomics will aid in the study of disease mechanisms, facilitate linkage analyses and provide candidate genes for study in veterinary as well as human patients.

References

1. Tripathi, R.C., *Ultrastructure of the exit pathway of the aqueous in lower mammals (a preliminary report on the "angular aqueous plexus")*. Exp Eye Res, 1971. 12: p. 311-314.
2. Bill, A., *Formation and drainage of aqueous humour in cats*. Exp Eye Res, 1966. 5: p. 185-190.
3. Samuelson, D.A., *Ophthalmic Anatomy*, in *Veterinary Ophthalmology*, K.N. Gelatt, Editor. 1999, Lippincott, Williams and Wilkins: Philadelphia. p. 31-150.
4. Bedford, P.G., *The aetiology of canine glaucoma*. Vet Rec, 1980. 107(4): p. 76-82.
5. Gelatt, K.N., D.E. Brooks, and D.A. Samuelson, *Comparative glaucomatology. I: The spontaneous glaucomas*. J Glaucoma, 1998. 7(3): p. 187-201.
6. Gelatt, K.N. and D.E. Brooks, *The Canine Glaucomas*, in *Veterinary Ophthalmology*, K.N. Gelatt, Editor. 1999, Lippincott Williams & Wilkins: Philadelphia. p. 701-754.
7. Pauli, A.M., et al. *Changes in intraocular pressure in dogs wearing a collar versus a harness*. in *34th Annual Conference of American College of Veterinary Ophthalmologists*. 2003. Coeur d'Alene, ID.
8. Smith, R.I.E., R.L. Peiffer, Jr., and B.P. Wilcock, *Some aspects of the pathology of canine glaucoma*. Prog Vet Comp Ophthalmol, 1993. 3(1): p. 16-27.
9. Gelatt, K.N. and E.O. MacKay, *Secondary glaucomas in the dog in North America*. Vet Ophthalmol, 2004. 7(4): p. 245-259.
10. Gibson, T.E., et al., *Comparison of gonioscopy and ultrasound biomicroscopy for evaluating the iridocorneal angle in dogs*. J Am Vet Med Assoc, 1998. 213(5): p. 635-638.
11. Aubin, M.L., et al., *Ultrasound biomicroscopy of the feline anterior segment*. Vet Ophthalmol, 2003. 6(1): p. 15-17.
12. Bentley, E., P.E. Miller, and K.A. Diehl, *Use of high-resolution ultrasound as a diagnostic tool in veterinary ophthalmology*. J Am Vet Med Assoc, 2003. 223(11): p. 1617-1622.
13. Miller, P.E., et al. *High resolution ultrasound imaging of the anterior segment of dogs with primary glaucoma prior to, and following the topical application of 0.005% latanoprost*. in *34th Ann Meeting Am Coll Vet Ophthalmol*. 2003. Coeur d'Alene, Idaho.
14. Miller, P.E., et al. *A clinical and ultrasonographic examination of the eyes of Bouvier des Flandres dog with and emphasis on identifying risk factors for primary angle closure glaucoma*. in *35th Annual Conference of the American College of Veterinary Ophthalmologists*. 2004. Washington, DC.
15. Deehr, A.J. and R.R. Dubielzig, *A histopathological study of iridociliary cysts and glaucoma in Golden Retrievers*. Vet Ophthalmol, 1998. 1(2-3): p. 153-158.
16. Spiess, B.M., et al., *Multiple ciliary body cysts and secondary glaucoma in the Great Dane: a report of nine cases*. Vet Ophthalmol, 1998. 1(1): p. 41-45.
17. Klaus, G., et al., *The causes of glaucoma in dogs: a morphological survey using a collection of 3980 canine ocular submissions*. Veterinary Ophthalmology, 2000. 3(4): p. 255.
18. Petersen-Jones, S.M. and J.R. Mould, *Chronic glaucoma in cairn terriers*. Vet Rec, 1991. 128(26): p. 619.
19. Petersen-Jones, S.M., *Abnormal ocular pigment deposition associated with glaucoma in the cairn terrier*. J Small Anim Pract, 1991. 32: p. 19-22.
20. van de Sandt, R.R.O.M., et al., *Abnormal ocular pigment deposition and glaucoma in the dog*. Vet Ophthalmol, 2003. 6(4): p. 273-278.
21. Ekesten, B. and K. Narfström, *Correlation of morphologic features of the iridocorneal angle to intraocular pressure in Samoyeds*. Am J Vet Res, 1991. 52(11): p. 1875-1878.
22. Read, R.A., J.L. Wood, and K.H. Lakhani, *Pectinate ligament dysplasia (PLD) and glaucoma in Flat Coated Retrievers. I. Objectives, technique and results of a PLD survey*. Vet Ophthalmol, 1998. 1(2-3): p. 85-90.
23. Bjerkas, E., B. Ekesten, and W. Farstad, *Pectinate ligament dysplasia and narrowing of the iridocorneal angle associated with glaucoma in the English Springer Spaniel*. Vet Ophthalmol, 2002. 5(1): p. 49-54.
24. Wood, J.L., K.H. Lakhani, and R.A. Read, *Pectinate ligament dysplasia and glaucoma in Flat Coated Retrievers. II. Assessment of prevalence and heritability*. Vet Ophthalmol, 1998. 1(2-3): p. 91-99.
25. Wood, J.L., et al., *Relationship of the degree of goniodysgenesis and other ocular measurements to glaucoma in Great Danes*. Am J Vet Res, 2001. 62(9): p. 1493-9.

26. Gelatt, K.N. and E.O. MacKay, *Prevalence of the breed-related glaucomas in pure-bred dogs in North America*. Vet Ophthalmol, 2004. 7(2): p. 97-111.
27. Martin, C.L., *Scanning electron microscopic examination of selected canine iridocorneal abnormalities*. J Am Anim Hosp Assoc, 1975. 11: p. 300-306.
28. Bedford, P.G., *The aetiology of primary glaucoma in the dog*. J Small Anim Pract, 1975. 16(4): p. 217-39.
29. Cottrell, B.D., *Primary glaucoma in the Welsh springer spaniel*. J Small Anim Pract, 1988. 29: p. 185-199.
30. Morrison, J.C. and E.M. Van Buskirk, *The canine eye: pectinate ligaments and aqueous outflow resistance*. Invest Ophthalmol Vis Sci, 1982. 23: p. 726-732.
31. Ekesten, B., et al., *Primary glaucoma in the Norwegian elkhound*. Vet Comp Ophthalmol, 1997. 7(1): p. 14-.
32. Oshima, Y., E. Bjerkas, and R.L. Peiffer Jr, *Ocular histopathologic observations in Norwegian Elkhounds with primary open-angle, closed-cleft glaucoma*. Vet Ophthalmol, 2004. 7(3): p. 185-188.
33. Ekesten, B., *Correlation of intraocular distances to the iridicorneal angle in Samoyeds with special reference to angle-closure glaucoma*. Prog Vet Comp Ophthalmol, 1993. 3(2): p. 67-73.
34. Ekesten, B. and K. Narfström, *Age-related changes in intraocular pressure and iridocorneal angle in Samoyeds*. Prog Vet Comp Ophthalmol, 1992. 2(1): p. 37-40.
35. Mapstone, R., *Mechanics of pupil block*. Br J Ophthalmol, 1968. 52: p. 19-25.
36. Woo, E.K., et al., *Ultrasound biomicroscopic quantitative analysis of light-dark changes associated with pupillary block*. Am J Ophthalmol, 1999. 127: p. 43-47.
37. Reilly, C.M., R. Morris, and R.R. Dubielzig, *Canine goniodysgenesis-related glaucoma: a morphologic review of 100 cases looking at inflammation and pigment dispersion*. Vet Ophthalmol, 2005. 8(4): p. 253-258.
38. Grozdanic, S.D., et al. *Comparative molecular profile of canine, rodent and human glaucomatous eyes*. in *36th Annual Conference American College of Veterinary Ophthalmologists*. 2005.
39. Gelatt, K.N., et al., *Clinical manifestations of inherited glaucoma in the beagle*. Invest Ophthalmol Vis Sci, 1977. 16(12): p. 1135-42.
40. Gelatt-Nicholson, K.J., et al., *Comparative Doppler imaging of the ophthalmic vasculature in normal Beagles and Beagles with inherited primary open-angle glaucoma*. Vet Ophthalmol, 1999. 2(2): p. 97-105.
41. Gelatt, K.N., et al., *Progressive changes in ophthalmic blood velocities in Beagles with primary open angle glaucoma*. Vet Ophthalmol, 2003. 6(1): p. 77-84.
42. Gum, G.G., K.N. Gelatt, and P.A. Knepper, *Histochemical localization of glycosaminoglycans in the aqueous outflow pathways in normal Beagles and Beagles with inherited glaucoma*. Prog Vet Comp Ophthalmol, 1993. 3(2): p. 52-57.
43. MacKay, E.O., et al. *Aqueous humor and trabecular meshwork myocilin in normal and POAG Beagles*. in *35th Annual Meeting of the American College of Veterinary Ophthalmologists*. 2004. Washington, DC.
44. Gelatt, K.N., et al. *Aqueous humor myocilin in dogs with glaucoma and cataract*. in *36th Annual Conference American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
45. Stone, E.M., et al., *Identification of a gene that causes primary open angle glaucoma*. Science, 1997. 275: p. 668-670.
46. Kersey, J.P. and D.C. Broadway, *Corticosteroid-induced glaucoma: a review of the literature*. Eye, 2005: p. 1-10.
47. Zhan, G.L., O.C. Miranda, and L.Z. Bitó, *Steroid glaucoma: corticosteroid-induced ocular hypertension in cats*. Exp Eye Res, 1992. 54(2): p. 211-8.
48. Bhattacharjee, P., et al., *Pharmacological validation of a feline model of steroid-induced ocular hypertension*. Arch Ophthalmol, 1999. 117(3): p. 361-4.
49. Gelatt, K.N. and E.O. MacKay, *The ocular hypertensive effects of topical 0.1% dexamethasone in beagles with inherited glaucoma*. J Ocul Pharmacol Ther, 1997. 14: p. 57-.
50. Brooks, D.E., et al., *Histomorphometry of the optic nerves of normal dogs and dogs with hereditary glaucoma*. Exp Eye Res, 1995. 60(1): p. 71-89.
51. Brooks, D.E., A.M. Komaromy, and M.E. Kallberg, *Comparative optic nerve physiology: implications for glaucoma, neuroprotection, and neuroregeneration*. Vet Ophthalmol, 1999. 2(1): p. 13-25.
52. Radius, R.L. and B. Bade, *Pressure-induced optic nerve axonal transport interruption in cat eyes*. Arch Ophthalmol, 1981. 99: p. 2163-2165.

53. Brooks, D.E., A.M. Komaromy, and M.E. Kallberg, *Comparative retinal ganglion cell and optic nerve morphology*. Vet Ophthalmol, 1999. 2(1): p. 3-11.
54. Whiteman, A.L., et al., *Morphologic features of degeneration and cell death in the neurosensory retina in dogs with primary angle-closure glaucoma*. Am J Vet Res, 2002. 63(2): p. 257-61.
55. McInay, T.R., et al., *Evaluation of glutamate loss from damaged retinal cells of dogs with primary glaucoma*. Am J Vet Res, 2004. 65(6): p. 776-786.
56. Madl, J.E., et al., *Depletion of taurine and glutamate from damaged photoreceptors in the retinas of dogs with primary glaucoma*. Am J Vet Res, 2005. 66(5): p. 791-799.
57. Wood, J.L.N., K.H. Lakhani, and W.E. Henley, *An epidemiological approach to prevention and control of three common heritable diseases in canine pedigree breeds in the United Kingdom*. Vet J, 2004. 168: p. 14-27.

The Feline Glaucomas

Gill McLellan

Clinical Features:

Glaucoma is relatively uncommon in the cat compared to the dog, although it is possible that many feline cases go unrecognized. Authors of a recent study suggested that around 1% of cats older than 7 years may be affected by glaucoma.^[1] In contrast to the situation in dogs, feline glaucoma is typically an insidious, gradually progressive disease. Moderate elevations in IOP are associated with few overt clinical signs and cats are frequently not presented for evaluation until late in the disease process.^[2-4] In one recent retrospective study, 73% of glaucomatous cats were blind at the time of initial presentation.^[3]

The most common clinical signs in cats with glaucoma are:

Mydriasis, which may lead to pronounced anisocoria in cases of unilateral glaucoma

Mild to moderate conjunctival hyperemia

Subtle corneal edema, that is seldom accompanied by pronounced neovascularization (unless severe Exposure keratopathy develops)

Buphthalmos, often with Haab's striae and exposure keratopathy.

Pupillary light reflexes may be slow and incomplete but tend to be preserved until late in the course of the disease process.

Posterior segment changes are also subtle, and the lack of myelination of the feline optic nerve head (ONH) renders "cupping" difficult to appreciate. A combination of both direct ophthalmoscopy and indirect ophthalmoscopy using an appropriate (e.g. 14-15D), lens may facilitate identification of subtle ONH cupping, a gray peri-papillary "halo" and increased prominence of the lamina cribrosa in affected cats. In young cats, the lamina cribrosa is relatively resilient and ONH cupping may be reversible. Some vision may be preserved in chronically glaucomatous cats despite gross buphthalmos.^[5,6] The authors of one published histopathologic study considered that the degree of inner retinal degeneration was relatively mild given the duration of glaucoma.^[7] However pronounced fundoscopic abnormalities, including diffuse increase in tapetal reflectivity, multifocal areas of altered pigmentation within the peripapillary tapetal fundus, and attenuation of the retinal vasculature, as well as ONH cupping and degeneration may be observed in cats with documented chronic glaucoma. In extreme buphthalmos, rhegmatogenous retinal detachment may also occur.

As discussed below, feline glaucoma is often secondary to other anterior segment disease and thorough ocular examination may identify subtle evidence of underlying disease, such as keratic precipitates, rubeosis iridis, intraocular masses or alteration in anterior chamber depth.^[3,4,8]

Causes of Feline Glaucoma:

Primary Glaucoma:

Spontaneous primary glaucoma is relatively rare in the cat.^[9] No other underlying cause for glaucoma could be identified in only 3/131 glaucomatous feline eyes that were examined histopathologically.^[7] Both open-angle glaucoma, in which no abnormalities of the iridocorneal angle or ciliary cleft could be identified, and glaucoma associated with pectinate ligament dysplasia, have been reported in adult cats.^[5, 7, 8, 10] Breeds that may be at increased risk of primary glaucoma include the Siamese, Burmese and Persian.^[2, 5, 8] In an Australian series of adult Burmese cats with primary glaucoma, iridocorneal angles appeared narrow or closed, although gonioscopy was often performed months or even years after initial diagnosis.^[5]

Congenital glaucoma:

A novel inherited form of primary congenital glaucoma has recently been identified in a pedigree of Siamese cats in the USA and a breeding colony has been established at Iowa State University to facilitate the characterization of this disease and development of a model for human congenital glaucoma. Gonioscopic findings are consistent with open or only slightly narrowed irido-corneal

angles, but high resolution ultrasonography (HRUS) and histopathology have revealed congenital abnormalities of the ciliary cleft and intrascleral venous plexus. The abnormalities identified are suggestive of “developmental arrest” in the normal processes of post-natal development of the aqueous outflow system.^[11] All affected cats have chronically elevated IOPs, with a dramatic accentuation of diurnal IOP range, and demonstrate bilateral buphthalmos at an early age. Secondary lens subluxation and spherophakia may be noted by 4 months of age in some cats.^[6,12] The associated optic neuropathy and retinal degeneration is slowly progressive, with vision retained until 2-4 years in most affected eyes. Preliminary data indicates that the disease is inherited as an autosomal recessive trait. However, a possible influence on disease expression by altered tyrosinase activity & consequently L-DOPA levels (responsible for the Siamese colour-point coat) has not yet been definitively excluded.^[13]

Sporadic cases of feline early-onset glaucoma associated with congenital ocular malformations, including microphakia, ectopia lentis, iridoschisis, pectinate ligament dysplasia, multiple iridociliary cysts and persistent pupillary membranes have been reported in the veterinary literature.^[8,14]

Secondary Glaucoma:

The majority of cases of feline glaucoma are secondary to other ocular disease.^[2-4,8] In a recent retrospective study of 82 glaucomatous cats, 81/93 eyes had clinical evidence of underlying ocular disease.^[3]

Uveitis:

Intraocular inflammation, particularly chronic lympho-plasmacytic uveitis, is the most frequently reported cause of glaucoma in cats and may lead to elevation of IOP through a number of different pathogenic mechanisms.^[2, 3, 7, 8, 15, 16] Pre-iridal fibrovascular membranes may compromise the iridocorneal angle by occlusion of the iridocorneal angle opening and synechiation, or aqueous outflow may be impeded by direct infiltration of the aqueous outflow pathway by inflammatory cells and/or inflammatory debris.^[7] Intraocular hemorrhage, particularly related to hypertensive ocular disease in elderly cats may also result in secondary glaucoma that is poorly responsive to medical therapy.

Neoplasia:

Intra-ocular neoplasia is another important cause of glaucoma in cats, as a result of obliteration of the aqueous outflow pathway by neoplastic cells and/or associated inflammation. Diffuse uveal melanoma, ocular lymphoma and ocular sarcoma are most frequently implicated in the pathogenesis of feline secondary glaucoma^[3, 7, 8]

Lens Associated Glaucoma:

Lens-associated glaucoma in cats may occur secondary to phacoclastic uveitis resulting from lens trauma.^[7, 16] Lens luxation in cats is most often secondary to glaucoma (rather than vice versa) or secondary to uveitis.^[17] Despite the fact that, in comparison to the situation in dogs, anterior lens luxation is seldom an underlying cause of acute glaucoma in the cat, removal of luxated lenses is still recommended for sighted eyes. Chronic anterior lens luxation is likely to result in loss of vision in the cat, due to development of corneal edema or secondary cataract, as well as glaucoma. Glaucoma may also occur in cats with intumescent cataract.^[8]

Feline Aqueous Humor Misdirection Syndrome:

An unusual form of glaucoma, characterized by a uniformly shallow anterior chamber, has recently been described in older cats.^[3, 18, 19] The disease typically follows an insidious course, affecting cats with a mean age of 11.7 years in the largest case series reported.^[19] An apparent gender predisposition was noted, as 24/32 affected cats in the series were female. In addition to a shallow anterior chamber, eyes affected by FAHMS often have dilated pupils, which results in anisocoria as the disease is frequently unilateral at the time of initial presentation. Visual impairment is common and may, at least in part, be related to a considerable myopic refractive shift due to anterior lens displacement (-10D to -16.5D in cats that were refracted). Ocular ultrasonography or histopathology reveals thickening of the anterior vitreous face, anterior displacement of the iris and lens, and clear spaces in the vitreous cavity. It has been postulated that aqueous humor is misdirected posteriorly, becoming trapped within “pools” in the vitreous cavity. Subsequently, anteriorly displaced vitreal elements become condensed, compressed and juxtaposed against the lens and ciliary processes. This juxtaposition is responsible for so-called “cilio-vitreous-lenticular block”, with elevation in IOP, collapse of the ciliary cleft and narrowing of the iridocorneal angle.^[19] Use of drugs that are associated with extreme miosis or

mydriasis is not recommended in cats with FAHMS as they may precipitate glaucomatous crises. Fortunately, clinical experience suggests that IOP can be maintained, at least within a comfortable range, by topical carbonic anhydrase inhibitors in affected cats, and surgical intervention (phacoemulsification and anterior vitrectomy) is seldom warranted.

References:

1. Kroll, M.M., P.E. Miller, and I. Rodan, *Intraocular pressure measurements obtained as part of a comprehensive geriatric health examination from cats seven years of age or older*. J Am Vet Med Assoc, 2001. 219(10): p. 1406-10.
2. Ridgway, M.D. and A.H. Brightman, *Feline glaucoma: a retrospective study of 29 clinical cases*. J Am Anim Hosp Assoc, 1989. 25: p. 485-490.
3. Blocker, T. and A. van der Woerd, *The feline glaucomas: 82 cases (1995-1999)*. Vet Ophthalmol, 2001. 4(2): p. 81-85.
4. Dietrich, U., *Feline Glaucomas*. Clin Tech Small Anim Pract, 2005. 20: p. 108-116.
5. Hampson, E.C., R.I. Smith, and M.E. Bernays, *Primary glaucoma in Burmese cats*. Aust Vet J, 2002. 80(11): p. 672-80.
6. McLellan, G.J., et al. *Congenital glaucoma in the Siamese cat- a new spontaneously occurring animal model for glaucoma research*. in *35th Annual Meeting of the American College of Veterinary Ophthalmologists*. 2004. Washington, DC.
7. Wilcock, B.P., R.L. Peiffer, Jr., and M.G. Davidson, *The causes of glaucoma in cats*. Vet Pathol, 1990. 27(1): p. 35-40.
8. Walde, I. and E. Rapp, *Feline glaucoma. Clinical and morphological aspects (a retrospective study of 38 cases)*. Eur J Compan Anim Pract, 1993. 4: p. 87-105.
9. Gelatt, K.N., D.E. Brooks, and D.A. Samuelson, *Comparative glaucomatology. I: The spontaneous glaucomas*. J Glaucoma, 1998. 7(3): p. 187-201.
10. Stadtbaumer, K., R.L. Peiffer, and B. Nell. *Goniodysgenesis associated with primary glaucoma in an adult European Shorthair cat: clinical and histopathological findings*. in *Annual Meeting of the European College of Veterinary Ophthalmologists and the European Society of Veterinary Ophthalmology*. 2005. Oporto, Portugal.
11. Richardson, T.M., et al., *A morphologic and morphometric analysis of the aqueous outflow system of the developing cat eye*. Experimental Eye Research, 1985. 41(1): p. 31-51.
12. McLellan, G.J., K. Sigle, and M.H. Kuehn. *Effect of topical 1% tropicamide on intraocular pressure in cats with primary congenital glaucoma*. in *36th Annual Meeting of the American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
13. Libby, R.T., et al., *Modification of ocular defects in mouse developmental glaucoma models by tyrosinase*. Science, 2003. 299(5612): p. 1578-81.
14. Brown, A., R. Munger, and R.L. Peiffer Jr, *Congenital glaucoma and iridoschisis in a Siamese cat*. Vet Comp Ophthalmol, 1994. 4(3): p. 121-124.
15. Coop, M.C. and J.R. Thomas, *Bilateral glaucoma in the cat*. J Am Vet Med Assoc, 1958. 133: p. 369-370.
16. McCalla, T.L., C.P. Moore, and L.L. Collier, *Phacoclastic uveitis with secondary glaucoma in a cat*. Compan Anim Pract, 1988. 2(11): p. 13-17.
17. Olivero, D.K., et al., *Feline lens displacement : a retrospective analysis of 345 cases*. Prog Vet Comp Ophthalmol, 1991. 1(4): p. 239-244.
18. La Croix, N., et al. *Feline malignant glaucoma/aqueous misdirection: 16 cases*. in *34th Ann Meeting Am Coll Vet Ophthalmol*. 2003. Coeur d'Alene, Idaho: Am Coll Vet Ophthalmol.
19. Czederpiltz, J.M.C., et al., *Aqueous humor misdirection syndrome as a cause of glaucoma in cats: 32 cases*. J Am Vet Med Assoc, 2005. in press.

What's New in the Management of Glaucoma?

Gill McLellan

Tremendous advances have been made in recent years in the management of canine and feline glaucoma.^[1] In particular, an increasing number of published studies involving both conventional and novel medical and surgical glaucoma therapies have enhanced the abilities of veterinary ophthalmologists to practice evidence-based medicine. When interpreting the findings of published studies, anatomical, physiological and pharmacological differences between species must be taken into account as should the heterogeneity of response within a given species or even individual patient. In particular, one should be cautious in extrapolating the results of studies conducted in normal subjects to clinical patients, given that the response of glaucomatous subjects to the same drug or procedure may be very different. Ideally, experimental study designs should take normal diurnal variations in IOP into account, and clinical trials should involve appropriate controls, randomization and be “blinded”.

When selecting an appropriate management strategy for the canine or feline glaucomas, the following are important considerations:

Is the glaucoma primary or secondary?

What are the specific mechanisms for IOP elevation?

Are these mechanisms reversible or irreversible?

What is the likely potential for vision in the affected eye?

What is the likelihood of owner and patient compliance?

Will the cost of proposed therapy be acceptable to the owner?

Is the contralateral eye at risk?

In essence, THERAPY SHOULD BE TAILORED TO THE INDIVIDUAL.

An important consideration when selecting an appropriate treatment strategy must be the underlying mechanism for IOP elevation. It is also recommended that, particularly in the management of acute congestive glaucoma, more than one component of aqueous humour dynamics should be targeted in order to maximise reduction in IOP. If we revisit the Goldmann equation, it becomes clear that using a drug that reduces aqueous production in combination with a drug that increases outflow should have a considerably greater impact on IOP than using a combination of two drugs that both target aqueous production.

MEDICAL THERAPY FOR GLAUCOMA

Agents that reduce aqueous production

Carbonic Anhydrase Inhibitors: For many years, oral carbonic anhydrase inhibitors (acetazolamide, methazolamide and dichlorphenamide) played a key role in the medical management of canine glaucoma. By reducing the secretion of bicarbonate ions, with sodium ions and secondarily water, into the posterior chamber, these drugs reduce aqueous humour formation and IOP. These agents were shown to have a dose-responsive effect, reducing IOP by an average of 7-28% in normal and glaucomatous dogs.^[2] However, significant systemic side-effects were commonly observed, at least in part related to hypokalaemia and metabolic acidosis. Systemic therapy has been largely superseded by the development of topical carbonic anhydrase inhibitors, dorzolamide (Trusopt, Merck) and brinzolamide (Azopt, Alcon). Concurrent use of topical and systemic carbonic anhydrase inhibitors does not appear to result in an additive IOP lowering effect in glaucomatous Beagles.^[3] Following topical application of dorzolamide 2%, three times daily, IOP in normal dogs was reduced by a mean of 24%.^[4] Administration of topical 1% brinzolamide led to a mean reduction in IOP of 3.5mmHg in one study involving normotensive dogs.^[5] One published study indicated that topical 1% Brinzolamide had no effect on IOP in normal cats.^[6] Topical application of 2% dorzolamide significantly reduced IOP in

normal cats by a mean of about 2mmHg.^[7] It is recommended that the currently available carbonic anhydrase inhibitors are applied three times daily. Therefore it is noteworthy that, in both these feline studies, the topical carbonic anhydrase inhibitor in question was only applied twice daily. In contrast, topical dorzolamide 2% applied three times daily reduced IOP in cats with primary congenital glaucoma by about 15mmHg and substantially dampened the pronounced diurnal fluctuations in IOP that are a characteristic of this disease.^[8] Conjunctival hyperemia and blepharitis have been reported in treated dogs. Cats treated with topical carbonic anhydrase inhibitors may show signs of inappetence and hypersalivation, perhaps related to an unpleasant taste. The topical formulation of brinzolamide may be better tolerated, with fewer local side-effects, than dorzolamide, as the former has a more physiologic pH.

Beta-blockers : Beta-blockers reduce IOP by inhibiting aqueous humour secretion. Twice daily application of timolol maleate lead to a modest reduction in IOP (mean 4-5mmHg in glaucomatous dogs) at commercially available concentrations (0.25 and 0.5%). The drug also significantly lowered heart rate when administered at higher, more effective concentrations, in both normal and glaucomatous dogs.^[9] When timolol is administered twice daily in combination with dorzolamide (Cosopt, Merck & Co. Inc) IOP is reduced to a greater extent (mean 8.4mmHg) than by three times daily administration of Dorzolamide alone (7.5mmHg).^[10] In normotensive cats, timolol reduces IOP by a mean of 22%. Miosis is also noted and can persist for up to a week in treated cat eyes.^[11] Topical application of the combined alpha-1 & Beta-blocker, nipradilol 0.25%, reduced IOP by a small but statistically significant amount, both by reducing aqueous production and enhancing outflow, in normal dogs, without any adverse cardiovascular effects.^[12]

Agents that increase aqueous outflow

Miotics: Agents in this class include direct acting cholinergic drugs such as pilocarpine and the longer acting acetylcholinesterase inhibitors, such as demecarium bromide and ecothiophate iodide. The indirect acting drugs have the advantage of both potency and prolonged duration of action (up to 55 hours) but unfortunately are no longer widely, commercially available. Cholinergic agents result in increased aqueous outflow by contraction of the sphincter pupillae and longitudinal ciliary muscles.^[13]^[14] Solutions of pilocarpine have a low pH and can be associated with ocular irritation. Topical application of 2% pilocarpine or 0.25% demecarium bromide led to a transient breakdown in the blood-ocular barrier of dogs.. The potential for these agents to intensify concurrent or underlying uveitis warrants careful consideration in this species.^[15] In normal cats treated with 2% pilocarpine, IOP was reduced by a mean of 15% in the treated eye, (maximal reduction of 30% at 4 hours). However, miosis and IOP reduction were also noted, albeit to a lesser degree, in the untreated eye, indicating the greater propensity for systemic absorption of topical drugs, and hence increased risk of systemic adverse effects, in cats. ^[16]

Use of miotics have found renewed favour in the USA both for the prophylactic treatment of “at-risk eyes” (see below) and in the prevention of post-operative ocular hypertension following cataract surgery in dogs. Intra-cameral injection of 0.01% carbachol (Miostat, Alcon) was found to abolish post-operative ocular hypertension following phacoemulsification cataract surgery in dogs.^[17] The efficacy of this therapy does not appear to be solely related to its miotic properties, as use of topical latanoprost, another potent miotic in dogs, did not consistently prevent post-operative ocular hypertension in a similar study.(P.E. Miller, personal communication) Miotic therapy may also delay the onset of lens luxation and secondary glaucoma in the contralateral eye of dogs with primary zonular instability, a use that was supported by results of a recent study.^[18]

Prostaglandins: Species differences in prostanoid receptor distribution and second messenger generation within different ocular tissues have major implications for the effects, and efficacy of topical prostaglandin analogue therapy for glaucoma. For example, intense miosis observed in dogs and cats is related to the presence of FP receptors in the iris sphincter of these species, compared to humans.^[19] The degree of miosis can be so pronounced that it can be visually disabling in some dogs, and is also a contraindication for use of these drugs in patients with the potential for pupil block by an anteriorly luxated lens or prolapsed vitreous.

The FP receptor agonists, including latanoprost 0.005% (Xalatan, Pharmacia) and travoprost 0.004% (Travatan, Alcon), and the prostamide bimatoprost (Lumigan, Allergan) have a potent IOP-lowering effect in dogs, in the range of 65-75% in glaucomatous dogs,^[20-22] but have no significant effect on IOP in normal cats.^[20, 23]

Although FP receptors are largely responsible for the effects of prostaglandin analogs on the canine and human ciliary body, EP receptors are predominantly responsible for relaxation of feline ciliary muscle.^[24, 25] Hence, with refinement of prostaglandin analogues to maximize their specificity for FP receptors on human ciliary body, in order to minimize adverse effects such as ocular inflammation, newly developed prostaglandin analogues are, unfortunately, less and less likely to have any direct ocular hypotensive effect in cats.

The mechanisms by which topical prostaglandins reduce IOP remain unclear.^[26] One proposed mechanism involves alteration of the extracellular matrix within the ciliary body tissue, enhancing uveoscleral outflow. This is associated with a maximal reduction in IOP in humans around 8-12 hours post-treatment. In glaucomatous dogs, however, dramatic and more rapid reduction in IOP may be observed. The rapidity of this response may reflect the reversal of pupillary block by the intense miosis observed following topical prostanoid therapy in this species. However, recent fluorophotometric studies in normal dogs have also documented a rapid and dramatic (average 93%) reduction in aqueous humour flow rates (i.e. aqueous formation) following treatment with 0.005% latanoprost.^[27] Although labeled for human use once daily, in dogs twice daily application of prostaglandin analogues, or application in the evening if only applied once daily, is recommended to minimize pronounced daily fluctuations in IOP.^[22, 28]

Alpha-2 adrenergic agonists: Although their precise mechanism of action is unclear, the alpha-2 agonists appear to be potent inhibitors of aqueous humor production in humans. Topical application of 0.5% apraclonidine (Iopidine, Alcon) led to a modest, 3mmHg reduction in IOP in normal dogs 8 hours post-treatment, and was associated with mild mydriasis.^[29] Apraclonidine 0.5% reduced IOP in normal cats by an average of 24% within 6 hours of treatment but also resulted in miosis that persisted up to 24 hours. Evidence of systemic toxicity following topical application of apraclonidine, including a mean reduction in heart-rate of about 12%, as well as vomiting that was noted in 8/9 cats treated with the drug, precludes its use in cats.^[30] Brimonidine 0.2% produced a statistically significant but small reduction in IOP in glaucomatous Beagles, in conjunction with mild miosis and reduction in heart rate, and is likely to be of little value as the sole agent in the medical management of canine glaucoma.^[31]

Prophylaxis: The evidence to support some form of prophylactic medical therapy in the contralateral “at-risk” eye of dogs with PACG is compelling. It has been shown that prophylactic topical therapy with either a combination of miotic and corticosteroid once daily (demecarium bromide 0.25% / betamethasone), or with the topical beta1-selective blocker betaxolol (0.5%) twice daily, can delay the onset of glaucoma in the “second eye” until around 30 months after initial diagnosis, compared with a median time of 8 months to the development of glaucoma in untreated eyes.^[32]

Monitoring: About 30% of dogs with previously diagnosed unilateral PACG will go on to develop glaucoma in the contralateral eye within a few months to years of diagnosis. Unfortunately, the limitations of IOP monitoring to identify “early” glaucoma in predisposed eyes were recently highlighted by a study which determined that 61% of dogs that were monitored prior to development of PACG in their second eye had IOP measurements consistently <20mmHg on every examination prior to the development of overt glaucoma.^[33] This may reflect variation in timing of tonometry within the study and also failure to consider the effect of mean diurnal range in IOP on development of acute angle closure, and preservation or loss of vision, as has been identified in human glaucoma patients.^[34] The value of UBM or HRUS monitoring for progressive changes in ciliary cleft morphology, or for retinoscopic evidence of progressive refractive errors, in predicting onset of PACG is currently under investigation.

The drugs don't work – time for surgical intervention?

Use of Nd:YAG or Diode LASER for transcleral cyclophotocoagulation has been shown to reduce IOP in normal and glaucomatous dogs and cats.^[35-41] However, post-operative IOP spikes, uveitis, hyphema, secondary cataract formation, ocular hypotension or persistent IOP elevation, are relatively common complications. Use of diode endoscopic cyclophotocoagulation has recently been described in dogs and cats with glaucoma. Direct visualization of the ciliary processes during treatment allows accurate delivery of LASER energy and verification of tissue response that can lead to a more predictable post-operative reduction in IOP. A limbal or pars plana approach may be used to introduce the intraocular endoscopic delivery device. Complications of this relatively invasive procedure included retinal detachment, intraocular hemorrhage and ocular hypotony.^[42] The relatively unpredictable response to LASER therapy and post-operative complications currently argue against the use of these cyclodestructive procedures as a prophylactic treatment in “at risk” eyes. Typically, these procedures are reserved for patients that are poorly responsive to medical treatment for glaucoma.

As with medical treatment, surgical strategies that combine procedures aimed at reducing aqueous humour production with procedures to enhance aqueous humour outflow appear to offer the greatest chance of success in the management of canine glaucoma. Although promising, the surgical implantation of drainage devices into the anterior chamber is accompanied by a relatively high complication rate. Placement of an Ahmed valved gonioimplant, in conjunction with anti-metabolite therapy, may lead to more successful control of IOP and retention of vision when combined with cyclodestructive procedures such as transcleral laser cyclophotocoagulation or cyclocryotherapy,^[43, 44] than when performed as a sole procedure.^[45-48]

Is there light at the end of the tunnel?

I have focused on interventions that target IOP and aqueous humor dynamics, either by affecting aqueous production, outflow, or both. Currently, these are the main mechanisms by which the clinician in practice can modify outcome in patients with glaucoma. Unfortunately, even adequate control of IOP, within a normal to low range, in glaucomatous animals does not necessarily prevent the progression of optic nerve and retinal degeneration once the cascade of cell death has been initiated.

A neuroprotective effect of systemic calcium channel blockers has been proposed but safety and efficacy of this treatment has not been established. However, in a cat model of axotomized retinal ganglion cells (a situation which mimics glaucomatous optic neuropathy) the combined intravitreal injection of the neurotrophic factors BDNF, CNTF, and forskolin (which increases intracellular cAMP), greatly enhanced retinal ganglion cell survival and axonal recovery from injury.^[49] Researchers at Iowa State University are currently investigating the ability of a novel intravitreal micro-bead drug delivery system to deliver neurotrophic factors to the retina and optic nerve of mice and dogs, prior to testing in dogs with acute glaucoma.

Given the delay in initial diagnosis of glaucoma that all too often occurs in dogs with PACG, the prognosis for vision is typically very poor in the first affected eye. Unfortunately, once mechanisms of cell death have been initiated in response to the severe IOP elevation that often occurs in dogs with PACG, degeneration of optic nerve and retina rapidly becomes irreversible. The “window of opportunity” during which we can intervene to promote cell survival and recovery is therefore an extremely narrow one. This accentuates the critical nature of client education and the need for consideration of prophylactic therapy for “at risk” eyes. Traditional emergency therapy for glaucoma, with osmotic agents such as Mannitol (1-2g/kg given intravenously as a 20% solution over 20 minutes), medical therapy with prostaglandin analogues, and even anterior chamber paracentesis, will likely remain an important part of our treatment strategy in many cases.

References

1. Willis, A.M., K.A. Diehl, and T.E. Robbin, *Advances in topical glaucoma therapy*. Vet Ophthalmol, 2002. 5(1): p. 9-17.
2. Gelatt, K.N., G.G. Gum, and L.W. Williams, *Ocular hypotensive effects of carbonic anhydrase inhibitors in normotensive and glaucomatous Beagles*. Am J Vet Res, 1979. 40: p. 334-345.
3. Gelatt, K.N. and E.O. MacKay, *Changes in intraocular pressure associated with topical dorzolamide and oral methazolamide in glaucomatous dogs*. Vet Ophthalmol, 2001. 4(1): p. 61-67.
4. Cawrse, M.A., D.A. Ward, and D.V. Hendrix, *Effects of topical application of a 2% solution of dorzolamide on intraocular pressure and aqueous humor flow rate in clinically normal dogs*. Am J Vet Res, 2001. 62(6): p. 859-63.
5. Whelan, N.C., et al. *A comparison of the efficacy of topical brinzolamide and dorzolamide alone and in combination with oral methazolamide in decreasing normal canine intraocular pressure*. in *30th Annual Meeting American College of Veterinary Ophthalmologists*. 1999. Chicago, IL.
6. Gray, H.E., A.M. Willis, and R.V. Morgan, *Effects of topical administration of 1% brinzolamide on normal cat eyes*. Vet Ophthalmol, 2003. 6(4): p. 285-290.
7. Rainbow, M.E. and J. Dziezyc, *Effects of twice daily application of 2% dorzolamide on intraocular pressure in normal cats*. Vet Ophthalmol, 2003. 6(2): p. 147-150.
8. Sigle, K.J., et al. *The effect of dorzolamide 2% on intraocular pressure in cats with primary congenital glaucoma*. in *36th Annual Meeting American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
9. Gum, G.G., et al., *The effect of topical timolol maleate on intraocular pressure in normal Beagles and Beagles with inherited glaucoma*. Prog Vet Comp Ophthalmol, 1991. 1(3): p. 141-149.
10. Plummer, C.E., E.O. MacKay, and K.N. Gelatt. *Comparison of the effects of topical administration of a fixed combination of dorzolamide-timolol to monotherapy with timolol or dorzolamide on IOP, pupil size and heart rate in glaucomatous dogs*. in *36th Annual Conference American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
11. Wilkie, D.A. and C.A. Latimer, *Effects of topical administration of timolol maleate on intraocular pressure and pupil size in cats*. Am J Vet Res, 1991. 52(3): p. 436-40.
12. Maehara, S., et al., *Effects of topical nipradilol and timolol maleate on intraocular pressure, facility of outflow, arterial blood pressure and pulse rate in dogs*. Vet Ophthalmol, 2004. 7(3): p. 147-150.
13. Gum, G.G., et al., *Tonographic effects of pilocarpine and pilocarpine-epinephrine in dogs*. J Small Anim Pract, 1993. 34: p. 112-116.
14. Gum, G.G., et al., *Effect of topically applied demecarium bromide and echothiophate iodide on intraocular pressure and pupil size in beagles with normotensive eyes and beagles with inherited glaucoma*. Am J Vet Res, 1993. 54(2): p. 287-93.
15. Krohne, S.G., *Effect of topically applied 2% pilocarpine and 0.25% demecarium bromide on blood-aqueous barrier permeability in dogs*. American Journal of Veterinary Research, 1994. 55(12): p. 1729-1733.
16. Wilkie, D.A. and C.A. Latimer, *Effects of topical administration of 2.0% pilocarpine on intraocular pressure and pupil size in cats*. Am J Vet Res, 1991. 52(3): p. 441-4.
17. Stuhr, C.M., et al., *Effect of intracameral administration of carbachol on the postoperative increase in intraocular pressure in dogs undergoing cataract extraction*. J Am Vet Med Assoc, 1998. 212(12): p. 1885-8.
18. Binder, D.R., I.P. Herring, and D.L. Ward. *Efficacy of prophylactic topical miotic treatment for spontaneous lens luxation in dogs*. in *35th Annual Meeting of American College of Veterinary Ophthalmologists*. 2004. Washington, DC.
19. Bhattacharjee, P. and C.A. Paterson, *Studies on prostanoid receptors in ocular tissues*. J Ocular Pharmacol, 1994. 10(1): p. 167-175.
20. Studer, M.E., C.L. Martin, and J. Stiles, *Effects of 0.005% latanoprost solution on intraocular pressure in healthy dogs and cats*. Am J Vet Res, 2000. 61(10): p. 1220-4.
21. Gelatt, K.N. and E.O. Mackay, *Effect of different dose schedules of bimatoprost on intraocular pressure and pupil size in the glaucomatous Beagle*. J Ocul Pharmacol Ther, 2002. 18(6): p. 525-34.
22. Gelatt, K.N. and E.O. MacKay, *Effect of different dose schedules of travoprost on intraocular pressure and pupil size in the glaucomatous Beagle*. Vet Ophthalmol, 2004. 7(1): p. 53-7.
23. Bartoe, J.T., et al., *The effects of bimatoprost and unoprostone isopropyl on the intraocular pressure in normal cats*. Vet Ophthalmol, 2005. 8(4): p. 247-252.

24. Chen, J. and D.F. Woodward, *Prostanoid-induced relaxation of precontracted cat ciliary muscle is mediated by EP2 and DP receptors*. Invest Ophthalmol Vis Sci, 1992. 33(11): p. 3195-3201.
25. Bhattacharjee, P., B.S. Williams, and C.A. Paterson, *Responses of intraocular pressure and the pupil of feline eyes to prostaglandin EP1 and FP receptor agonists*. Invest Ophthalmol Vis Sci, 1999. 40(12): p. 3047-53.
26. Weinreb, R.N., et al., *Effects of prostaglandins on the aqueous humor outflow pathways*. Surv Ophthalmol, 2002. 47(Suppl 1): p. S53-64.
27. Ward, D. *Effects of latanoprost on aqueous humor flow rate in normal dogs*. in *36th Annual Conference American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
28. Gelatt, K.N. and E.O. MacKay, *Effect of different dose schedules of latanoprost on intraocular pressure and pupil size in the glaucomatous Beagle*. Vet Ophthalmol, 2001. 4(4): p. 283-288.
29. Miller, P.E., M.J. Nelson, and S.L. Rhaesa, *Effects of topical administration of 0.5% apraclonidine on intraocular pressure, pupil size, and heart rate in clinically normal dogs*. Am J Vet Res, 1996. 57(1): p. 79-82.
30. Miller, P.E. and S.L. Rhaesa, *Effects of topical administration of 0.5% apraclonidine on intraocular pressure, pupil size, and heart rate in clinically normal cats*. Am J Vet Res, 1996. 57(1): p. 83-6.
31. Gelatt, K.N. and E.O. MacKay, *Effect of single and multiple doses of 0.2% brimonidine tartrate in the glaucomatous Beagle*. Vet Ophthalmol, 2002. 5(4): p. 253-262.
32. Miller, P.E., et al., *The efficacy of topical prophylactic antiglaucoma therapy in primary closed angle glaucoma in dogs: a multicenter clinical trial*. J Am Anim Hosp Assoc, 2000. 36(5): p. 431-8.
33. Sandberg, C.A. and P.E. Miller. *Intraocular pressure screening in dogs predisposed to primary angle closure glaucoma*. in *36th Annual Conference American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
34. Asrani, S., et al., *Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma*. J Glaucoma, 2000. 9(2): p. 134-42.
35. Nasisse, M.P., et al., *Neodymium:yttrium, aluminum, and garnet laser energy delivered transsclerally to the ciliary body of dogs*. Am J Vet Res, 1988. 49(11): p. 1972-8.
36. Nasisse, M.P., et al., *Treatment of glaucoma by use of transscleral neodymium:yttrium aluminum garnet laser cyclocoagulation in dogs*. J Am Vet Med Assoc, 1990. 197(3): p. 350-4.
37. Sapienza, J.S., et al., *Contact transcleral cyclophotocoagulation using Neodymium:Yttrium Aluminum Garnet laser in normal dogs*. Prog Vet Comp Ophthalmol, 1992. 2(4): p. 147-.
38. Rosenberg, L.F., et al., *Cat model for intraocular pressure reduction after transscleral Nd:YAG cyclophotocoagulation*. Curr Eye Res, 1995. 14(4): p. 255-61.
39. Cook, C.S., *Surgery for glaucoma*. Vet Clin North Am Small Anim Pract, 1997. 27(5): p. 1109-29.
40. Cook, C., et al., *Diode laser transscleral cyclophotocoagulation for the the treatment of glaucoma in dogs: results of six and twelve month follow-up*. Vet Comp Ophthalmol, 1997. 7(3): p. 148-154.
41. Hardman, C. and R.G. Stanley, *Diode laser transscleral cyclophotocoagulation for the treatment of primary glaucoma in 18 dogs: a retrospective study*. Vet Ophthalmol, 2001. 4(3): p. 209-15.
42. Bras, I.D., et al. *Diode endoscopic cyclophotocoagulation in canine and feline glaucoma*. in *36th Annual Conference American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
43. Bentley, E., et al., *Combined cycloablation and gonioimplantation for treatment of glaucoma in dogs: 18 cases (1992-1998)*. J Am Vet Med Assoc, 1999. 215(10): p. 1469-72.
44. Sapienza, J.S. and A. van der Woerd, *Combined transcleral diode laser cyclophotocoagulation and Ahmed gonioimplantation in dogs with primary glaucoma: 51 cases (1996-2004)*. Vet Ophthalmol, 2005. 8(2): p. 121-127.
45. Bedford, P.G.C., *A clinical evaluation of a one-piece drainage system in the treatment of canine glaucoma*. J Small Anim Pract, 1989. 30: p. 68-75.
46. Tinsley, D.M. and D.M. Betts, *Clinical experience with a glaucoma drainage device in dogs*. Vet Comp Ophthalmol, 1994. 4(2): p. 77-.
47. Bentley, E., et al., *Implantation of filtering devices in dogs with glaucoma: preliminary results in 13 eyes*. Vet Comp Ophthalmol, 1996. 6(4): p. 243-.
48. Cullen, C.L., *Cullen frontal sinus valved glaucoma shunt: preliminary findings in dogs with primary glaucoma*. Vet Ophthalmol, 2004. 7(5): p. 311-318.
49. Watanabe, M. and Y. Fukuda, *Survival and axonal regeneration of retinal ganglion cells in adult cats*. Prog Retin Eye Res, 2002. 21(6): p. 529-553.

Equine squamous cell carcinoma

Derek C Knottenbelt, OBE, BVM&S, DVMS, DipECEIM, MRCVS,
University of Liverpool, Leahurst, Neston, Wirral. CH64 7TE
email: knotty@liv.ac.uk

Primary squamous cell carcinoma is a common tumour of horses that is restricted to squamous epithelium. Within the broad pathological group there is wide variation in the prevalence of each type mainly relating to the anatomical location.

Solar radiation, geographical location, and individual susceptibility (which may relate to breed, age and lack of adnexal pigment) are probably the most important risk factors associated with SCC.

Squamous cell carcinoma (SCC) occurs in the eyelids, the conjunctiva (particularly of the third eyelid and the lateral limbus of the eye) and on the surface of the cornea (carcinoma in situ). Palpebral SCC (SCCp) is often extensive, highly destructive, and invasive. However, a milder proliferative, slower growing form is sometimes encountered. Non-pigmented eyelids are much more liable to develop the destructive and ulcerative form and certain breeds seem more liable to its development. Although for the most part SCC of the eyelids and orbital structures are very seldom malignant they can cause extensive destruction or infiltration and so treatment becomes progressively more problematical.

The least common ocular forms include a lateral limbal SCC (SCCl) that is invariably proliferative (at least until the condition is advanced) and carcinoma in situ (SCCis) where the corneal epithelium is involved. The latter are sometimes difficult to diagnose. Usually cases are presented for investigation of ocular discharges (usually with a characteristic purulent appearance)

A particularly invasive and aggressive form of SCC occurs in the nasal chambers, the paranasal sinuses or the hard palate and can cause exophthalmos in aged horses.

From a purely clinical perspective three forms can be recognised.

Proliferative form in which the tumour develops in a proliferative fashion. The earliest forms are sometimes described as pre-carcinomatous squamous papilloma. Lateral limbal and carcinoma in situ are invariably proliferative. Often they produce significant keratin and so are usually relatively well-differentiated. This possibly explains why the majority of tumours at these sites are not highly malignant.

Ulcerative / Destructive forms that result in tissue loss and erosions and ulcerations. These are commonly found for example on the non-pigmented eyelids and third eyelids. Combined ulcerative / Destructive forms are actually quite common and are common the nictitans and eyelid regions.

Malignant behaviour is rare but can be very dangerous. Nictitans forms appear to be the most liable to malignancy and failure to remove the whole mass, or neglected tumours that are allowed to extend into the conjunctiva and orbit may metastasise into pharyngeal and parotid lymph nodes. Tumours may even extend from here into the nasal cavity but again it may be difficult to confirm the path of development in some cases.

Diagnosis:

A careful clinical examination is essential because the early clinical signs are not usually distinctive. One of the characteristic features of the palpebral, conjunctival and nictitans forms of SCC is a persistent sticky mucopurulent ocular discharge. In the early stages. Haemolacrimation is a feature and testing the tears with a urine blood dipstick usually reveals blood – although of course there are some other causes of this also! When changes are advanced diagnosis is usually simple.

Subtle lymph node enlargement may be overlooked but from a prognostic perspective this is clearly vital. In all cases of palpebral, nictitans and limbal carcinoma the ipsilateral guttural pouch should be

examined endoscopically. The pharyngeal lymph nodes can be directly examined and it is sometimes possible to visually identify carcinoma in the affected glands.

Pathological diagnosis of all the forms is easily achieved by biopsy but some sites such as the cornea are not amenable to excision of large pieces of tissue so pathologists need to be informed of the nature of the lesion and the location of the biopsy within it. Where profound cellular changes and a significant sample / biopsy can be collected the chances of a successful diagnosis is more likely.

The histological characteristics are typical and easily recognised and the extent of malignancy is likewise easily recognised by the extent of differentiation and the character / normality (or otherwise) of the keratin production. Scrapes taken from the surface of proliferative or ulcerative lesions or fine needle aspirates can be diagnostic but require a skilled cytohistopathologist.

Management:

Palpebral SCC (SCCp) is often extensive, highly destructive, and invasive. However, a milder proliferative, slower growing form is sometimes encountered. Although for the most part SCCp and conjunctival SCC (SCCc) structures are seldom malignant they can cause extensive destruction or infiltration and so treatment becomes progressively more problematical.

The conventional management of squamous cell carcinoma relies upon surgical removal or cryonecrosis, where these are feasible or to the application of various antimetabolic and cytotoxic chemicals. Radiation is the gold standard of therapy in suitable sites where surgical removal cannot be contemplated or where the tumour margins cannot be defined sufficiently to allow total removal. There are no immunological methods for the management of SCC.

Benign neglect is ill advised for this condition. Surgical excision is a realistic proposition for nictitans, conjunctival and in situ corneal forms but the criteria for selection of this method in and around the eye are strict. Eyelid tumours are seldom amenable to this option, but very small, localised proliferative lesions can be excised if the margin of the lid can be preserved or can be reconstructed satisfactorily to preclude the complications arising from poor eyelid function. Squamous cell carcinoma of the upper and lower eyelids can be treated by surgical excision/debulking combined with cryotherapy or brachytherapy. Laser surgery has been used but it is too early to assess the overall long-term success rate.

Surgical ablation should not be contemplated if the tumour has already invaded the local lymph node or there are difficulties with margin definition.

Every piece of tissue removed from a surgical site should be submitted for histopathology. If the tumour is reported to extend beyond the excisional margin then a repeat surgery or adjunctive methods such as radiation or topical 1% 5-fluoro-uracil could be used.

There is no excuse in modern practice for the crude scissor amputation of the nictitans that is unfortunately commonly practiced. The initial results may seem acceptable but infections, scarring, prolapse of the retrobulbar fat and future risks of corneal pathology make this a last resort to be used only where anaesthetic safety or financial constraints preclude quality surgery.

Cryosurgery has been used for nictitans, limbal, and carcinoma in situ with variable successes. Cryonecrosis is rarely effective for palpebral SCC or conjunctival SCC. Results dependent on the efficiency of tumour ablation. Thermocouple assistance is strongly advised to minimise the risks of unwanted cell damage. There are circumstances where cryosurgery is totally impossible.

5-Fluoro-uracil ointment has been described for oral SCC (Patterson, 1997) but there are no reports of its use in the eyelids or for ocular lesions. A 1% ophthalmic solution of 5-F-U has been used by the author to treat a small limbal carcinoma that regrew at the site of a previous surgical excision but the true nature of the lesion (carcinoma V granuloma) was never established pathologically.

Topical ophthalmic 5-fluorouracil can be a useful adjunctive therapy following surgical removal of conjunctival or corneal carcinomas.

Intralesional infiltration of an emulsion of cisplatin in almond (or sesame) oil or a stable emulsion containing a higher concentration of cisplatin (up to 10 mg / ml) can be used. It is effective in some cases although there are few reports of efficacy compared to other standard methods.

Immunomodulation using BCG has little effect (in contrast to the similar bovine condition).

Radiation: All forms of SCC are very susceptible to both gamma and beta radiation and so it is the 'gold standard' for all forms of SCC in the horse. The cosmetic effects of the treatment are remarkably good with a relatively rapid resolution and minimal secondary complications even in severely destructive eyelid cases.

Prognosis:

The prognosis for squamous cell carcinoma is dependent on:

The site of the lesion and its suitability for any effective therapy

The malignancy of the tumour itself

The duration of the lesion

The number of failed attempts to treat it

The extent of secondary consequences arising from the tumour.

The prognosis is poor if periocular and/or orbital tissues have been invaded. This is seldom a rapidly growing tumour type and so it is disappointing if a case is presented in an advanced stage that precludes treatment. Because for the most part SCC in the horse has less malignancy than in most other species (although gastric carcinoma, oropharyngeal carcinoma and penile carcinoma in younger geldings are usually (but not invariably!) far more malignant than the other forms), there is usually time to consider the best available treatment options.

Pathologists will be able to identify the extent of differentiation of the squamous cells from the amount and nature of the keratin production – undifferentiated potentially malignant cells usually have less keratin production than the benign forms. The other issue that is usually established pathologically is the margin of excision where this is used as treatment. Failure to excise the whole tumour will result in recurrence.

Typically of any neoplastic disease the prognosis is heavily dependent on the time interval between onset and diagnosis.

Prevention:

Prevention of the ophthalmic forms is a possibility. Where horses are noted during pre-purchase examination or other routine examinations, to have non-pigmented eyelids, third eyelids or lateral limbal conjunctivae, the owner can be advised to take precautionary measures such as avoiding high UV sunlight or wearing of a UV protector mask. Horses that have developmental non-pigmented skin around the eyes (vitiligo and Pinky Arab Syndromes, scarring and radiation induced leucoderma) are also more liable to carcinoma at the site.

Breeding from suitably pigmented parents (possibly with long eyelashes too!) will minimise the risks but no matter how pigmented some horses are they still may develop carcinoma at any of the susceptible sites.

The future?

Tumour markers would seem to be the future hope for early diagnosis but as yet no specific (or non-specific) marker has yet been identified for horses. Until we have methods for early diagnosis and better treatments (with radiation teletherapy being the best overall future option) the periocular and ocular forms of SCC is likely to provide both a diagnostic challenge and a therapeutic problem.

Equine Periocular Sarcoid

A potential problem for every veterinarian!

Derek C Knottenbelt OBE, Dip ECEIM BVM&S, DVM&S, MRCVS

Introduction: The equine sarcoid is a fibroblastic neoplasm sometimes (but not invariably) with secondary keratinocyte effects that arise from cytokines and growth factors expressed by the tumour cells.

The disease affects all breeds of horse, mules, donkeys and zebra and the majority of cases are first presented between 2 and 9 years of age. Several genetic lines have known predisposition but individuals within those lines may not get sarcoids at all while others may be severely affected. The Lipizzaner is reported to be unaffected. The Quarterhorse is reported to be less susceptible, while the Arabian is more so.

The anatomical and logistic complications associated with periocular sarcoids make their management a particular challenge¹. Sarcoid has a high propensity for recurrence and frequently becomes more aggressive if subject to accidental or iatrogenic interference. The course of the condition is entirely unpredictable.

Recognition

Six distinctive types can be recognized in the periocular region but the specific types may not be clearly identifiable in every case.

Occult sarcoid appears as hairless, often roughly circular (at least in the early stages) areas. One or more small cutaneous (palpable) nodules (2-5 mm diameter) or roughened areas with a mild hyperkeratotic appearance can usually be identified.

Occult sarcoid has been regularly mistaken for dermatophytosis.

Verrucous (warty) sarcoid have a rough hyperkeratotic appearance and scaling over limited or wider areas of the body. The skin is thickened and lacks natural flexibility. The latter has significance in the periorbital skin because the eyelids may be less efficient.

The verrucose sarcoid can be mistaken for papillomatosis (true warts), chronic blistering, cheloid or hypertrophic scarring, [severe] chronic rubbing or irritation such as in sweet itch or habronemiasis),

Nodular sarcoids are easily recognisable, as firm, well-defined cutaneous or subcutaneous, spherical nodules of 5-20 mm diameter (but they can be much larger). Type A nodules lie under apparently normal skin and may be moved independently of the skin and the deeper structures. Pathologically they have a loose fibro-connective tissue capsule. Type B nodules have dermal and sometimes deep attachments, which prevent independent movement. The sub-classification is important because treatment options are different for the two types.

The eyelids and periorbital skin are common sites where their numbers can vary widely. They can be mistaken for insect bites, foreign body reactions, melanoma and other neoplastic masses, skin cysts and collagen granuloma.

Fibroblastic sarcoid have a characteristic fleshy appearance. They are divisible into two subgroups. Type 1 are pedunculated (i.e. they have a narrow neck) while Type 2 are broad based (sessile). Both forms are commonly encountered around the eye. .

Fibroblastic sarcoids do not metastasize. Repeated insult (accidental or iatrogenic) encourages further local sub-dermal and dermal invasion; around the eye this is a potential disaster .

This type of sarcoid looks very like exuberant granulation tissue but it is really difficult to mistake it for anything else.

Mixed (Verrucous, Nodular and Fibroblastic) Sarcoid probably represents a progressive/transient state between the verrucous / occult types and fibroblastic / nodular types. Variations in proportion of the several types of sarcoid are infinite. They become progressively more aggressive as more fibroblastic transformation takes place following ill-advised biopsy or injury.

Malignant / Malevolent Sarcoid ² is a particularly dangerous form in the immediate area around the eye. The malevolent form of sarcoid is particularly dangerous, not least because there is no current treatment t. Its appearance is not easily mistaken for other skin diseases but again the presence of several different types of sarcoid elsewhere on the body makes the diagnosis relatively simple. .

Confirmation of Diagnosis:

Most affected horses have more than one lesion. Multiple tumors with characteristic features of the various types of sarcoid on an individual horse make the diagnosis simple - there are no other diseases with the same range of clinical features and types. Some veterinary surgeons are understandably reluctant to interfere with a sarcoid because interference may trigger a massive and uncontrollable expansion of the lesion.

Treatment:

The best possible / available treatment method should follow as soon after diagnosis as possible. It may be better to leave the lesion untreated than to interfere with an inadequate method that has little or no chance of resolving the lesion.

The prognosis is always very guarded. Scarring and distortion of the upper eyelid in particular, damage to the nasolacrimal duct and secondary effects of the treatment to ocular structures can arise. Owners must be made aware of the limitations, cost and likely/possible outcome of the various treatment options before embarking upon any treatment.

Factors that influence choice of treatment:

The number, types and exact location of the lesions

The eyelids have serious limitations in the tolerance of some treatments. A lesion on the eyelid that looks superficial and benign may in fact be extremely dangerous but may also be relatively innocuous. There is no way of identifying which behaviour an individual lesion will take on.

The relative value of the animal and the cost of treatment.

Treatment is always expensive and may need to be repeated several times. Many owners will expect treatment regardless of the relative value of the horse.

Previous treatments and history.

The prognosis for treatment is significantly worse if an unsuccessful treatment attempt has been made previously. Repeated failures make the prognosis very poor. The first attempt at treatment should be directed therefore at the best available option with the highest chance of success.

Complication through coexistence of other factors such as granulation tissue, infection, fly-strike or other tumors at the same site etc.

These may alter both the histological and clinical appearance and may be misleading. Infection is a particular problem in ulcerated or traumatized sarcoid.

Facilities and practicality of the available treatment option.

The best option may be economically or practically impossible. For example radiation carries a good prognosis but is very restricted, requiring special conditions.

Treatment Methods:

Many treatment methods have been used with varying success. Treatment must remove every single abnormal cell - leaving even one behind will inevitably, sooner or later, result in return of the tumour (often with a more aggressive form).

Ligation: A ligature of nylon thread, a rubber band (or even a tail hair) may be used around the base of the lesion to cut off its blood supply. This method is probably contraindicated unless the margins of the sarcoid can be accurately defined.

Surgical excision: There is a high rate of recurrence in all except the most confined and defined lesions following surgical excision. The failure rate can be explained by the atypical deep extensions that are commonly encountered in periocular sarcoids of all types. Knottenbelt and Kelly (2000)³ confirmed that penetration of the sarcoid into the palpebral musculature is the norm rather than the exception. Superficial (occult and verrucose) lesions can be effectively treated by wide excision provided that the wound can be closed and then protected during healing. The prognosis following surgery can be improved somewhat by combining it with other modalities such as cryosurgery, topical cytotoxic compounds, intralesional cisplatin injections or radiation

Cryosurgery (Freezing): Cryosurgery is commonly employed. While some veterinary surgeons have good success rates it has relatively poor overall success rates (except in the smallest and most defined lesions, which carry a reasonable success rate).

Laser surgery (CO₂-YAG laser excision): Laser excision has a relatively high success rate but again selection of the most appropriate lesions is very important. Around the eye this method has much to commend it although there are still major reservations about performing surgery at all in this location. It should be restricted to the lower lid and areas away from the major musculature of the upper eyelid.

Cytotoxic compounds: These induce extensive tissue necrosis and scarring. They are easy to apply and relatively cheap. Some complex mixtures of these with antimetabolic, corticosteroid and cytotoxic drugs have a reasonable reputation. Because of the special difficulties of treatment of periocular lesions, these are seldom indicated for periocular lesions.

Tazarotene: The synthetic acetylenic retinoid tazarotene has proven a valuable aid in the management of periocular sarcoid. Its main role lies in its ability to reestablish normal apoptosis in keratinocytes that are adversely influenced by mediators secreted from transformed fibroblasts.

Intralesional 5-fluorouracil: Repeated intralesional injections of a 1% solution can be a helpful adjunct to prior surgical debulking. It is seldom effective on its own except for relatively small localised sarcoids.

Cisplatin: Good results are reported for small fibroblastic and nodular lesions in particular but it requires repeated injection into the lesion itself. It can be used in conjunction with surgical debulking. The material is very dangerous to humans.

Vaccines: Vaccines made from pieces of the tumours are illogical and contraindicated..

Immunomodulation: Proteins including various types of protein cell-wall fractions derived from Bacillus Calmette-Guérin (BCG) have been used widely for many years. This method works best with nodular lesions around the eye but away from the immediate peri-ocular region and in other types of sarcoid there is less obvious benefit. A side issue of this method is the occurrence of very alarming (and possibly even fatal allergic reactions) that may occur within minutes or hours of injection.

Radiation: Radiation is by far the most successful treatment but it is extremely expensive and has limited availability.

Homeopathic remedies are (expectedly) very disappointing but some natural substances including *Allo Vera*, Rosemary Oil and Teatree Oil may help a few cases. 'Exterra' (Indian Mud/ Blood root extract) has been used widely and some cases may respond. An undefined material known as *Camrosa* is, in my opinion, potentially dangerous – any material that will treat almost any disease in almost any animal must be viewed with some skepticism. In some cases application of remedies of various natural and homeopathic types have caused dramatic exacerbation.

Summary:

The equine sarcoid should be regarded as a form of skin cancer and should be treated seriously in every case; early veterinary consultation will help! Treatment at an early stage when there are few small sarcoids is in my opinion the best approach. The best possible treatment should be used for each individual lesion taking into account the type, anatomical location, duration, previous treatment history and owners resources. No effective method is cheap and none is certain of success – if we can resolve 50% of lesions we are doing exceptionally well. No matter how identical two lesions may appear to be, the response to treatment can be very different - no two cases respond in an identical fashion to a single treatment method.

Knottenbelt DC and Kelly DF (2000) Management of the periocular sarcoid: a report of the clinical and pathological findings of 450 cases. *Veterinary Ophthalmology*, 3

Knottenbelt DC, Edwards SER and Daniel EA (1995) The diagnosis and treatment of the equine sarcoid *In Practice* (supplement to *Veterinary Record*) 17: 123-129

Ophthalmic Tips **Gill McLellan**

Below are some clinical tips I've learned from friends, colleagues, mentors and residents.... or simply things I've learned (and continue to learn) "the hard way". These may, or may not, be written in textbooks or papers, and you may, or may not, find them novel or helpful.

Clinical Examination Techniques:

Always be thorough – stick to the same routine, the things you miss could be of no consequence....alternatively, they could be pivotal in your diagnosis and management strategy.

Take photographs whenever you can (you can almost always make time!). Try to review your photographs and case notes promptly – the "retrospectoscope" is a valuable and underused tool.

If you don't have a slit-lamp biomicroscope, buy one! (Although you can still "get by" if you learn to take full advantage of your direct ophthalmoscope's many mysterious functions....)

If you do have a slit-lamp, cherish it and use it properly! The examination room should be dark. Ensure that the oculars are adjusted before each use to bring the finest slit into sharp focus. A focusing bar should be bought or constructed if you don't have one. To appreciate the most subtle aqueous flare "shorten" the slit beam, which can usually be achieved by selecting a beam setting mid-way between the "cobalt blue" and "bright white".

Use an established, well-defined semi-quantitative scale to grade clinical features, such as aqueous flare and cell, wherever possible. Although these scales do not eliminate subjective differences in interpretation they represent an improvement over "mild" and "severe".^[1]

Be aware of the limitations of tonometry. Tonometers provide only "readings", which may or may not be representative of actual IOP. In any case, high IOP doesn't necessarily signify a diagnosis of glaucoma, low IOP doesn't necessarily exclude a diagnosis of glaucoma.

When performing indirect ophthalmoscopy, don't forget the less glamorous, non-tapetal fundus! A 2.2 Volk Panretinal lens will facilitate evaluation of the ora ciliaris retinae – stuff happens out there too.

So you've mastered indirect ophthalmoscopy? Don't forget the value of the direct ophthalmoscope when evaluating the optic nerve head, nerve fiber layer and smaller vessels in the peripapillary region.

I use the red-free (i.e. green!) filter a lot....try it, you may like it!

Don't underestimate the impact that species differences in globe optical properties will have on ophthalmoscopic appearance.^[2]

Buy a dim red light for your exam room – the scotopic obstacle course can provide valuable information about retinal function (...or not).

Learn how to perform retinoscopy. Refractive errors can impact performance in working dogs in particular and should be checked for.

Read the instruction manual for every piece of equipment you use or own. I'm not kidding!

Surgical Tips:

Read a textbook about microsurgical technique (such as Eisner's "Eye Surgery, an Introduction to Operative Technique, published by Springer-Verlag) at least once a year. For a really humbling experience critique your own surgical skills after doing so.

Spend time observing more experienced colleagues and physician ophthalmologists whenever you can. Although the latter in particular can be a humbling experience, bear in mind that our "human" counterparts are highly specialized in fairly narrow sub-specialties of ophthalmology....and have patients who direct their gaze on command.

Do not over-complicate things! Complex blepharoplastic procedures may look exciting in the textbooks but are seldom indicated. Many canine eyelid tumours are benign, but are often accompanied by a degree of associated inflammation. For this reason, try treating large tumours with anti-inflammatory therapy before embarking on radical excision and complex reconstructive procedures.

Do not over-simplify things! Canine entropion is a common but complex disorder and there may be more than one adnexal abnormality contributing to entropion in any individual dog. Thus, every case should warrant careful pre-operative evaluation and a “customized” approach.

When suturing the eyelid margin, progressively “trap” the suture tags in the subsequent knots, to help direct them away from the ocular surface and make suture removal a breeze.

After excision of abnormal, scrolled third eyelid cartilage, performing a third eyelid flap will help to prevent recurrence by “splinting” the cartilage against the globe as it heals.

If you use a microscope (for anything involving cornea or intraocular structures you should be...) ensure that you pay close attention to set-up. Make sure that table-height, patient’s head position and chair are adjusted for your optimal comfort. Don’t rush because you feel pressured to get started! Centre X-Y if you have it. Make sure that focus is set at a neutral position on the scope. Adjust the inter-pupillary distance. Manually focus scope. Ensure oculars are at a comfortable position. Zoom in to highest power, focus (e.g. on individual RBCs in a conjunctival vessel), adjust oculars (dominant eye first), zoom out, adjust oculars again (slight adjustment will likely be necessary to ensure “parfocality”). You should not need to accommodate to focus, as this is bad technique and a recipe for a headache! Note your settings for inter-pupillary distance and oculars for future reference.

Be aware of the potential for photic retinopathy, especially in aphakes – switch off the microscope lamp, or use appropriate filters, when the ‘scope isn’t being used...every second counts.

A lamellar keratectomy should result in a clear(ish) cornea. The most common cause of a sub-optimal post-operative outcome is failure to achieve and maintain a single plane of dissection between lamellae. Unfortunately, this is more difficult to achieve in a diseased cornea than in a normal cornea. Corneal trephines may be too small but use one whenever you can. Don’t stop and start. A Martinez corneal dissector is easier for the novice to use than a scalpel blade.

Consider using a bi-pedicle conjunctival flap to provide a good vascular supply if you are concerned about the health of the cornea to be grafted, or integrity of the conjunctival vascular supply, if the site to be grafted is distant from the limbus, or the defect is linear. This technique allows you to get away with a narrow flap – while avoiding necrosis that may occur at the devitalized leading edge of an advanced or rotated single pedicle flap. A strip of conjunctiva is harvested from the dorsal or lateral bulbar conjunctiva, but retaining its connection to adjacent conjunctiva at both ends. The flap can then be placed over the cornea like a “bucket handle” and anchored with sutures to the site of the defect. Trim pedicles under topical anesthesia later, as you would for a typical rotational flap.

When performing corneo- conjunctival or corneo–scleral transposition, try to transpose from the ventral limbus if possible for better cosmesis and visual function.

If using porcine S.I.S as a graft material for deep corneal defects, use two or more layers to provide enhanced support.

Don’t glue a Descemetocoele...and don’t try to suture them directly

Visco-elastic does more than simply maintaining an anterior chamber and protecting the endothelium during intra-ocular surgery. It’s a great “instrument”, e.g. slowing down the movement of foreign bodies in the anterior chamber, disrupting synechiae, etc. Just don’t forget to remove it from the anterior chamber afterwards.

Evisceration with intrascleral prosthesis implantation should definitely be considered as an option for blind canine eyes with primary glaucoma, provided the cornea is relatively healthy and tear production is normal. In my hands, this has a more predictable and more cosmetic outcome than intra-vitreal gentamycin and is cheaper than long-term medical therapy to control IOP in end-stage glaucoma.

Seek the advice of others...preferably before entering the operating theatre.

Understand that sometimes “better is the enemy of good”!

References

1. Hogan, M.J., S.J. Kimura, and P. Thygeson, *Signs and Symptoms of Uveitis: I. Anterior uveitis*. *Am J Ophthalmol*, 1959. 47(5, part II): p. 155-170.
2. Murphy, C.J. and H.C. Howland, *The optics of comparative ophthalmoscopy*. *Vision Res*, 1987. 27(4): p. 599-607.

Nutrition and the Eye

Gill McLellan

Although nutrition plays a vital role in ensuring the health and function of essentially every ocular structure, this review will focus on the impact of diet and dietary supplements on the retina. The importance of dietary sufficiency in a number of key nutrients has been recognized for many years. Deficiencies of vitamin E, vitamin A, and amino acids, in particular taurine, have been linked to ocular disease in companion animals. In some “at-risk” individuals, and those with signs of deficiency disease, further supplementation may be valuable. Clear evidence to support high dose supplementation of certain key vitamins and minerals, beyond levels normally consumed in a “healthy diet” or in conventional dietary supplements, is presently quite sparse. However, recently published work provides compelling evidence in support of supplementation and modifications to dietary polyunsaturated fatty acid (PUFA) content, particularly pre-natally and during early post-natal development of the visual system.

In the past 10-15 years there has been growing interest in antioxidants and their adversary “oxidative stress”. Nowhere are the effects of oxidative stress more readily apparent than in the eye, where oxidative damage has been implicated in a wide variety of pathological processes, in particular retinal disease and cataract. The pharmaceutical / “nutriceutical” industry has bombarded us, as clinicians and as consumers, with an overwhelming array of nutritional supplements. However, strong clinical and scientific data to define their indications, demonstrate beneficial effects in support of their use, and confirm an absence of adverse effects are sparse. It is important that we strive to apply the principles of evidence-based medicine, by integrating the best research evidence available, our clinical expertise in diagnosing disease, and the well-being of our patients together with the concerns and expectations of their owners.

Mechanisms for oxidative stress in the eye

The mammalian retina represents an extremely oxidative environment, in which high levels of metabolic and phagocytic activity within the neurosensory retina and RPE, abundant mitochondria, high local oxygen tension and high levels of exposure to incident light contribute to the generation of reactive oxygen species.^[1] These reactive species, including singlet oxygen, superoxide, hydrogen peroxide and hydroxyl radical are produced in abundance within the retina and, if unchecked, can lead to cell damage by oxidising membrane fatty acids, damaging DNA and modulating the activity of nucleotide cyclase.^[2] The retinal tissues are particularly vulnerable to oxidative damage because of the extremely high content of polyunsaturated fatty acids (PUFA) in their membrane lipids. It follows that a high anti-oxidant capacity is important to maintenance of the integrity of the RPE and neurosensory retina, particularly as these non-dividing cells are required to function for the lifetime of the animal. A variety of intracellular and extracellular defense mechanisms serve to protect the retina from the actions of reactive oxygen species and free radicals. Protective mechanisms that have characterized in the vertebrate retina include vitamin E, ascorbate, carotenoids, glutathione, catalase, superoxide dismutase, and both selenium-dependent and non-selenium-dependent glutathione peroxidase.^[1] The latter group of anti-oxidant enzymes play an important role in protection against less reactive species, such as superoxide and hydrogen peroxide. In contrast, the major lipid soluble anti-oxidant vitamin E is important in protecting against the highly reactive species such as hydroxyl and peroxy radicals within the lipid-rich environment of biological membranes. Vitamin E, of which the most biologically active form is alpha-tocopherol, reacts with and thereby “quenches” free-radicals about 100-fold faster than the membrane’s PUFA would.^[3, 4] It should be noted that a tocopheroxyl radical is formed during this “chain-breaking” reaction, and this in turn requires important hydrogen donors, such as ascorbate and thiols like glutathione, to allow regeneration to vitamin E.^[5-7] Failure of the complex interactions that regenerate alpha-tocopherol from the tocopheroxyl radical may account for its potentially deleterious pro-oxidant effects. Important roles for vitamin E in the maintenance of normal retinal function

include: protection of vitamin A, that forms part of the visual pigment rhodopsin, from oxidation; stabilization of cellular and intracellular membranes; protection of PUFA and maintenance of the membrane fluidity that is essential to the movement of molecules within photoreceptor membranes during the process of phototransduction, and also normal ion transport.^[7-13]

Lipid peroxidation is known to play an important role in the pathogenesis of many degenerative retinal disorders, including Age-related Macular Degeneration (AMD) and diabetic retinopathy in humans, as well as the retinopathy associated with vitamin E deficiency in humans and animals.

Vitamin E deficiency Retinopathy

Low plasma levels of vitamin E due to dietary deficiency have been associated with a very characteristic retinopathy in dogs. The clinical and pathological features of Retinal Pigment Epithelial Dystrophy (RPED, formerly known as central progressive retinal atrophy) are essentially identical to those of vitamin E deficiency. Accumulation of tan-coloured lipopigment within the RPE (visible ophthalmoscopically as light patches or spots throughout the tapetal fundus) is associated with multifocal to diffuse degeneration of the neurosensory retina.^[14-19] Preliminary studies in RPED affected Briards and Polish Lowland Sheepdogs identified low plasma vitamin E concentrations.^[20, 21] The role of vitamin E deficiency in the pathogenesis of RPED has since been clearly established, specifically in the English Cocker spaniel breed.^[22] Profound vitamin E deficiency was identified as a familial trait in this breed, with mean plasma vitamin E concentration of only 1.14µg/ml in affected dogs, compared with 20.15µg/ml in normal dogs. Unfortunately by the time of presentation, retinal changes are likely to be irreversible, therefore benefits of supplementation in terms of improvement in vision may not be demonstrable. However, supplementation is still warranted, even in dogs with advanced retinal degeneration, as they are at risk of developing an even more disabling neurologic syndrome. Neurological signs, including ataxia, proprioceptive deficits and weakness, were detected in 11 of 15 vitamin E deficient English Cocker spaniels.^[23] As the underlying defect in affected dogs involves abnormal transport and delivery of vitamin E to the tissues, rather than gastro-intestinal malabsorption, dietary supplementation with alpha-tocopherol can correct the plasma, and hopefully the associated tissue, deficiency. Currently, high dose supplementation with alpha-tocopherol (60-90iu/kg bodyweight) is recommended, based on the results of oral vitamin E tolerance tests. Frequent administration, at least twice or three times daily, is typically required, as relatively short-lived chylomicrons are likely to be the main mechanism for plasma delivery of vitamin E to the tissues in affected dogs. While subjective improvement was noted in response to treatment, complete resolution of neurological and visual signs is not expected in adult dogs.^[24] In the English Cocker spaniel breed, screening of fasted plasma vitamin E concentrations in young dogs may be warranted in order to identify affected individuals prior to the development of clinical signs.

Similar ocular and neurological abnormalities, and an association with low plasma vitamin E levels, have been identified in horses with motor neuron disease and degenerative encephalomyelopathy.^[25-30]

Vitamins - if nutritional deficiency causes disease, is “more” better?

When making recommendations regarding diet and supplementation, we should be cognizant of the risks involved in extrapolating from data regarding dietary requirements, absorption, transport, metabolism and storage of nutrients between species. To give an example, the unique inability, or limited capacity, of cats to synthesize taurine from dietary precursors such as methionine or cysteine is now well known. Clinical features of dietary taurine deficiency, including a characteristic retinopathy as well as cardiomyopathy, are well documented and commercially available feline diets should, in theory, all now contain adequate levels of taurine – although individual cats differ widely in their susceptibility to taurine deficiency.^[31-36]

Humans and guinea pigs, unlike most other mammals, are unable to make their own vitamin C and are totally reliant on dietary sources but signs of deficiency are extremely unlikely in other species. The protective effects of vitamin C in the lens has been widely investigated but the role of supplementation in prevention or amelioration of cataract remains controversial. Just 400mg/day, in adult humans, will saturate plasma and cells but there have been no confirmed adverse effects at intakes up to 2g/day.^[37]

Vitamin A supplementation (15,000 IU/day) with retinyl palmitate may slightly reduce the rate of retinal function decline in human retinitis pigmentosa, a group of photoreceptor degenerations similar to

generalized progressive retinal atrophy in dogs.^[38] Based on the results of a number of studies, there are concerns in humans that dietary supplementation with vitamin A may increase the risk of lung cancer, particularly in smokers.^[37] While this may be of little concern in our patient population, this scenario illustrates the need for careful risk:benefit analysis prior to making recommendations concerning dietary supplements! Experimental vitamin A deficiency has been associated with signs of visual impairment, papilledema and neurologic abnormalities in dogs, but this is unlikely to present a clinical problem in pets fed “normal” diets.^[39] In contrast, hypervitaminosis A has been described in both dogs and cats, in which skeletal abnormalities and weight loss are consistent features, and could be a concern if owners administer excessive supplements.^[40]

Trace elements

Selenium is known to be an important trace element, as selenoproteins have critical functions throughout the body, and in the retina seleno-enzymes such as glutathione peroxidase play an important role in protection against oxidative damage. However, even tiny excesses of selenium can be toxic, due to the propensity for excess selenium to start redox cycling which promotes oxidative damage, and have been shown to actually cause cataract in laboratory animals.^[41] An upper limit for daily intake of 400µg has therefore been suggested for adult humans. Safe upper limits for supplementation in dogs have not been determined despite the fact that the “therapeutic window” is very small for this trace element.

Zinc is required for the function of many different enzymes and is also has an important role in the structure and function of proteins and cell membranes. Zinc is vital to normal growth and development and immune function. Associations between zinc intake and retinal degenerations in humans have been investigated but results have been equivocal. Supplemental iron or calcium may impair zinc absorption however, high supplemental zinc intakes can reduce intestinal copper absorption leading to copper deficiency and this may, in turn, affect iron metabolism.^[37] We must be aware that such complex interactions between nutrients can contribute to deleterious effects in response to high dose supplementation. In essence, for some nutrients at least, there is a potential that “too much of a good thing” could lead to adverse effects if supplementation is excessive.

Fashionable Functional Foods -Carotenoids and Flavonoids

Although increasingly “fashionable”, the risks and benefits of these compounds are still being evaluated worldwide. Carotenoids are naturally occurring pigments that include beta-carotene, lutein, zeaxanthin and lycopene. Carotene is converted in the body into vitamin A (retinol) which is vital for normal visual function. Aside from the value of beta-carotene as a dietary source of vitamin A, carotenoids predominantly have an important anti-oxidant role, as they are extremely effective “quenchers” of singlet oxygen. Lutein and zeaxanthin are perhaps best known as important absorptive pigments that may filter out the “blue light hazard” to the human macula and may reduce photo-oxidative damage in the lens that contributes to age-related cataract.^[42]

Flavonoids are a group of thousands of distinct plant-derived phenolic compounds, or “phytochemicals”, the medicinal properties of which have been the subject of huge amounts of research over the past decade. Potential beneficial effects of flavonoids in prevention of ocular disease could be related to their ability to scavenge various oxidative species, although they may stabilize membranes by reducing fluidity of the lipid component, which of course could have a negative impact on phototransduction. Flavonoids may also have anti-inflammatory activity, by inhibiting the COX and/or lipo-oxygenase pathways, and also limit the oxidative modification of lipids by macrophages, that occurs in atherosclerosis.^[37] Although this latter effect is probably a lesser consideration in our veterinary patients, we may wish to consider that flavonoids in red wine may be responsible for the “French Paradox”, which defies the normally strong correlation between high intakes of saturated fats and incidence of coronary heart disease!

What about us? Nutrition and Age-related Macular Degeneration

AMD is the leading cause of vision loss in developed countries. About 50-80 million people worldwide are estimated to be currently affected by the intermediate to advanced stages of AMD. With a shift towards increasing life span and resulting aging population, the incidence of this disabling condition is likely to increase. Characteristic clinical features include the formation of drusen (Bruch’s membrane / sub-RPE deposits), altered macular pigmentation, choroidal neovascularization and resultant exudation and hemorrhage. The Age-related Eye Disease Study, AREDS, was initiated in the USA by the

National Institutes of Health, in order to evaluate the effects of high dose supplementation with vitamins C and E, beta-carotene, and zinc (to which cupric oxide was added to reduce the risk of copper deficiency) on progression of AMD. A slight but significant odds reduction for progression to advanced AMD was found in patients supplemented with vitamins C and E, beta-carotene and zinc in combination.^[43] Unfortunately, the study did not evaluate other carotenoids, including the macular pigments lutein and zeaxanthin, and did not evaluate other risk factors such as atherosclerosis and its association with hypercholesterolaemia, or complement factor H genetic variation.

In the absence of sufficient data to allow evidence-based recommendations, high dose vitamin and mineral supplementation is currently not recommended for the human population at large.^[44] At this time, it would seem appropriate to take a similarly cautious stance when making nutritional recommendations to the pet-owning public regarding supplementation of their animals' diets.

Polyunsaturated fatty acids and the eye - getting the balance right

An important exception to this very cautious approach relates to recommendations regarding dietary supplementation with polyunsaturated fatty acids (PUFA). A wealth of basic scientific and clinical evidence has been compiled over the past decade or two that supports the important role of (n-3) PUFAs in development of the brain and retina. Docosahexaenoic acid (DHA, or 22:6(n-3) is the most highly unsaturated PUFA, and also the predominant PUFA in photoreceptor membranes.^[45] High PUFA content and degrees of unsaturation allow relative membrane fluidity required for structural changes, required to allow "activated rhodopsin" (*all-trans* retinal) to interact with transducin molecules in the process of phototransduction. The functional significance of this was demonstrated by feeding "fat-free" diets to rats, which led to a pronounced reduction in ERG a- and b-wave amplitudes, with recovery noted on repletion of (n-3) PUFA.^[46]

Abnormal plasma levels of DHA have been reported in human retinitis pigmentosa patients,^[47] and similar findings were also reported in Miniature poodles and Abyssinian cats with inherited retinal degenerations.^[48, 49] It was disappointing to learn that, despite increases in DHA and other (n-3) fatty acids in liver and plasma in fish-oil supplemented dogs, supplementation did not modify disease phenotype and progression in canine progressive rod-cone degeneration.^[50] Supplementation of DHA (1200mg/day) did not slow the rate of visual field sensitivity over a 4 year period in human Retinitis Pigmentosa patients that had been taking vitamin A prior to entering the study.^[51] A demonstrable slowing of decline in visual function was, however, detected in patients who had not previously been taking vitamin A.^[52]

Neural and retinal development, begin during gestation and continue after birth in many species. Long chain PUFAs such as DHA are rapidly incorporated into neural and retinal tissues during this process and are essential for normal development. Dietary supplementation of dogs with marine fish oil, containing significant amounts of DHA, during pregnancy and lactation led to significant improvement in a variety of ERG parameters in puppies at 12 weeks of age, including threshold for scotopic ERG response.^[53] Supplementation of (n-3) PUFAs should perhaps be considered in pregnant and nursing animals, particularly those of working or sporting breeds in which optimal development of visual function and task learning behaviour could potentially have a significant impact on the future performance of their pups.

Other postulated beneficial effects of dietary omega-3 fatty acids involve neuroprotective effects that show promise in the management of ischemia/reperfusion injury, and their potential to compete with (n-6) PUFAs to reduce harmful inflammatory processes. Omega-3 fatty acids predominate in marine fish oils (e.g. derived from salmon or tuna), while (n-6) PUFA's predominate in seed oils that tend to be incorporated in animal feeds. Canine diets with precise alterations in their balance of (n-3):(n-6) PUFAs, result in significant increases in plasma (n-3) fatty acids and decreases in plasma n-6:n-3 ratios with significantly lower plasma arachidonic acid levels. This alteration in plasma PUFA profile likely shifts the balance of PUFA metabolism away from damaging eicosanoid production and consequently this diet is already marketed to aid in the management of tissue inflammation and discomfort in dogs with degenerative joint disease.(Hill's Prescription Diet Canine j/d, Hill's Pet Nutrition, Inc.) The impact of this dietary modification on inflammatory processes elsewhere in the body has not yet been determined.

References

1. Handelman, G.J. and E.A. Dratz, *The role of antioxidants in the retina and the retinal pigment epithelium and the nature of pro-oxidant induced damage*. Advances in Free Radical Biology and Medicine, 1986. 2: p. 1-89.
2. Newsome, D.A., et al., *Antioxidants in the retinal pigment epithelium*. Progress in Retinal and Eye Research, 1994. 13(1): p. 101-123.
3. Gallo-Torres, H.E., *Part 5: Biochemistry*, in *Vitamin E - A Comprehensive Treatise*, L.J. Machlin, Editor. 1980, Marcel-Dekker Inc.: New York. p. 169-372.
4. Kagan, V.E. and Y.Y. Tyurina, *Recycling and redox cycling of phenolic antioxidants*. Annals of the New York Academy of Sciences, 1998. 854: p. 425-434.
5. Sies, H., *Relationship between free radicals and vitamins: an overview*. International Journal of Vitamin and Nutrition Research Supplement (Switzerland), 1989. 30: p. 215-223.
6. Traber, M.G., *Cellular and molecular mechanisms of oxidants and antioxidants*. Mineral and Electrolyte Metabolism, 1997. 23: p. 135-139.
7. Wang, X. and P.J. Quinn, *Vitamin E and its function in membranes*. Progress in Lipid Research, 1999. 38(4): p. 309-336.
8. Robison, W.G., Jr., T. Kuwabara, and J.G. Beiri, *Deficiencies of vitamins E and A in the rat. Retinal damage and lipofuscin accumulation*. Investigative Ophthalmology and Visual Science, 1980. 19(9): p. 1030-1037.
9. Robison, W.G.J., T. Kuwabara, and J.G. Bieri, *The roles of vitamin E and unsaturated fatty acids in the visual process*. Retina, 1982. 2(4): p. 263-281.
10. Diplock, A.T., *The role of vitamin E in biological membranes*, in *Biology of Vitamin E*. 1983, Pitman Books Ltd.: London. p. 45-55.
11. Moran, J., P. Salazar, and H. Pasantes-Morales, *Effect of α -tocopherol and taurine on membrane fluidity of retinal rod outer segments*. Experimental Eye Research, 1987. 45: p. 769-776.
12. Goss-Sampson, M.A., T. Kriss, and D.P. Muller, *Retinal abnormalities in experimental vitamin E deficiency*. Free Radical Biology and Medicine, 1998. 25(4-5): p. 457-462.
13. Goss-Sampson, M.A., D.P.R. Muller, and A. Kriss, *Abnormalities of the electroretinogram and visual-evoked potential in vitamin E deficient rats*. Experimental Eye Research, 1991. 53: p. 623-627.
14. Parry, H.B., *Degenerations of the dog retina VI. Central progressive atrophy with pigment epithelial dystrophy*. British Journal of Ophthalmology, 1954. 38: p. 653-668.
15. Hayes, K.C., J.E.J. Rousseau, and D.M. Hegsted, *Plasma tocopherol concentrations and vitamin E deficiency in dogs*. Journal of the American Veterinary Medical Association, 1970. 157: p. 64-71.
16. Aguirre, G.D. and A. Laties, *Pigment epithelial dystrophy in the dog*. Experimental Eye Research, 1976. 23: p. 247-256.
17. Riis, R.C., et al., *Vitamin E deficiency retinopathy in dogs*. American Journal of Veterinary Research, 1981. 42(1): p. 74-86.

18. Lightfoot, R.M., et al., *Retinal pigment epithelial dystrophy in Briard dogs*. Research in Veterinary Science, 1996. 60: p. 17-23.
19. Davidson, M.G., et al., *Retinal degeneration associated with vitamin E deficiency in a group of hunting dogs*. Journal of the American Veterinary Medical Association, 1998. 213(5): p. 645-651.
20. Watson, P., *A Study of Retinal Pigment Epithelial Dystrophy in Dogs With Special Reference to Aspects of Plasma Lipoprotein Metabolism*, in *Department of Small Animal Medicine and Surgery, Royal Veterinary College*. 1993, University of London.
21. Watson, P., K. Narfström, and P.G.C. Bedford. *Retinal Pigment Epithelial Dystrophy (RPED) in Polish Lowland Sheepdogs*. in *British Small Animal Veterinary Association Congress*. 1993. Birmingham: BSAVA.
22. McLellan, G.J., et al., *Vitamin E deficiency in dogs with retinal pigment epithelial dystrophy*. The Veterinary Record, 2002. 151: p. 663-667.
23. McLellan, G.J., et al., *Clinical and pathological observations in English cocker spaniels with primary metabolic vitamin E deficiency and retinal pigment epithelial dystrophy*. The Veterinary Record, 2003. 153: p. 287-292.
24. McLellan, G.J., et al. *Vitamin E deficiency in canine retinal pigment epithelial dystrophy (RPED) - results of the oral vitamin E tolerance test in clinically normal dogs and in RPED affected Cocker spaniels*. in *WSAVA, BSAVA and FECAVA World Congress*. 1997. Birmingham, UK: BSAVA.
25. Divers, T.J., et al., *Equine motor neuron disease: findings in 28 horses and proposal of a pathophysiological mechanism for the disease*. Equine Veterinary Journal, 1994. 26(5): p. 409-415.
26. Blythe, L.L., et al., *Serially determined plasma a-tocopherol concentrations and results of the oral vitamin E absorption test in clinically normal horses and in horses with degenerative encephalomyelopathy*. American Journal of Veterinary Research, 1991. 52(6): p. 908-911.
27. Blythe, L.L., et al., *Vitamin E deficiency as a causative factor in equine degenerative myeloencephalopathy*. Annals of the New York Academy of Sciences, 1989. 570: p. 415-416
28. de la Rúa-Domenech, R., et al., *Association between plasma vitamin E concentration and the risk of equine motor neuron disease*. The Veterinary Journal, 1997. 154(3): p. 203-213.
29. Cummings, J.F., et al., *Endothelial lipopigment as an indicator of a-tocopherol deficiency in two equine neurodegenerative diseases*. Acta Neuropathologica, 1995. 90: p. 266-272.
30. Riis, R.C., et al., *Ocular manifestations of equine motor neuron disease*. Equine Veterinary Journal, 1999. 31(2): p. 99-110.
31. Schmidt, S.Y., E.L. Berson, and K.C. Hayes, *Retinal degeneration in cats fed caseine. I. Taurine deficiency*. Invest Ophthalmol, 1976. 15(1): p. 47-52.
32. Berson, E.L., et al., *Retinal degeneration in cats fed casein. II. Supplementation with methionine, cysteine or taurine*. Invest Ophthalmol, 1976. 15(1): p. 52-58.
33. Schmidt, S.Y., et al., *Retinal degeneration in cats fed casein. III. Taurine deficiency and ERG amplitudes*. Invest Ophthalmol, 1977. 16(7): p. 673-678.
34. Aguirre, G.D., *Retinal degeneration associated with the feeding of dog foods to cats*. Journal of the American Veterinary Medical Association, 1978. 172(7): p. 791-796.
35. Barnett, K.C. and I.H. Burger, *Taurine deficiency retinopathy in the cat*. Journal of Small Animal Practice, 1980. 21: p. 521-534.

36. Leon, A., W.R. Levick, and M.G. Sarossy, *Lesion topography and new histological features in feline taurine deficiency retinopathy*. *Exp Eye Res*, 1995. 61(6): p. 731-41.
37. Schreier, P., *Chemoprotective compounds in the diet*, in *Nutrition and the Eye. Basic and Clinical Research*, A. Augustin, Editor. 2005, Karger: Basel. p. 1-58.
38. Berson, E.L., et al., *A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa*. *Archives of Ophthalmology*, 1993. 111: p. 761-772.
39. Tvedten, H.W. and C.K. Whitehair, *Torulopsis glabrata and vitamin A deficiency in dogs*. *Am J Vet Res*, 1977. 38(12): p. 1941-1948.
40. Cho, D.Y., et al., *Hypervitaminosis A in the dog*. *Am J Vet Res*, 1975. 36(11): p. 1597-1603.
41. Flohe, L., *Selenium, selenoproteins and vision*, in *Nutrition and the Eye. Basic and Clinical Research*, A.J. Augustin, Editor. 2005, Karger: Basel. p. 89-102.
42. Stahl, W., *Macular carotenoids: lutein and zeaxanthin*, in *Nutrition and the Eye. Basic and Clinical Research*, A.J. Augustin, Editor. 2005, Karger: Basel. p. 70-88.
43. AREDS Research Group, *A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9*. *Arch Ophthalmol*, 2001. 119(10): p. 1439-52.
44. Schmidt-Erfurth, U., *Nutrition and Retina*, in *Nutrition and the Eye. Basic and Clinical Research*, A.J. Augustin, Editor. 2005, Karger: Basel. p. 120-147.
45. Anderson, R.E., et al., *Polyunsaturated fatty acids of photoreceptor membranes*. *Experimental Eye Research*, 1974. 18: p. 205-213.
46. Bourre, J.-M., et al., *The effects of dietary α -linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats*. *J Nutr*, 1989. 119: p. 1880-1892.
47. Anderson, R.E., et al., *Abnormal plasma levels of polyunsaturated fatty acid in autosomal dominant retinitis pigmentosa*. *Experimental Eye Research*, 1987. 44: p. 155-159.
48. Anderson, R.E., M.B. Maude, and R. Alvarez, *Plasma lipid abnormalities in the miniature poodle with progressive rod-cone degeneration*. *Exp Eye Res*, 1991. 52: p. 349-355.
49. Anderson, R.E., M.B. Maude, and S.-E. Nilsson, *Plasma lipid abnormalities in the Abyssinian cat with a hereditary rod-cone degeneration*. *Exp Eye Res*, 1991. 53: p. 415-417.
50. Aguirre, G.D., et al., *Diets enriched in docosahexaenoic acid fail to correct progressive rod-cone degeneration (prcd) phenotype*. *Invest Ophthalmol Vis Sci*, 1997. 38(11): p. 2387-407.
51. Berson, E.L., et al., *Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment*. *Arch Ophthalmol*, 2004. 122: p. 1297-1305.
52. Berson, E.L., et al., *Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. Subgroup analyses*. *Arch Ophthalmol*, 2004. 122: p. 1306-1314.
53. Heinemann, K.M., et al., *Long-Chain (n-3) Polyunsaturated Fatty Acids Are More Efficient than α -Linolenic Acid in Improving Electroretinogram Responses of Puppies Exposed during Gestation, Lactation, and Weaning*. *J. Nutr.*, 2005. 135(8): p. 1960-1966.

Equine Uveitis – What’s New?

Gill McLellan

Background:

Equine Recurrent Uveitis (ERU) is one of the commonest causes of blindness in horses, and as such is a major health concern and source of economic loss in this species. It is important for us to be aware that not all cases of uveitis in horses are attributable to ERU. Systemic disease or local trauma may lead to uveitis and careful general physical and ocular examination is therefore warranted in every case.

Clinical signs include corneal edema, miosis, aqueous flare, iris darkening, atrophy of the corpora nigra, posterior synechiae, cataract, vitreous haze or degeneration, retinal detachment and chorioretinopathy. Signs of discomfort, including increased lacrimation, apparent periocular swelling and blepharospasm are variable. “Typical” cases of ERU tend to be characterized by a relapsing course of acute or chronic episodes of intra-ocular inflammation of variable duration and severity. These episodes of inflammation are interspersed by intervening periods of quiescence but episodes tend to become more frequent and severe. Unfortunately this results in loss of vision in a significant proportion of cases, with over 50% of horses estimated to be blind within 2 years of diagnosis of ERU. However, in a sub-group of horses, in particular the Appaloosa, the disease can be more insidious in onset and the animal’s owner may not have recognized signs of altered ocular appearance or of discomfort until cataract, secondary glaucoma or phthisis bulbi are noted. It appears, albeit anecdotally, that significant posterior uveitis, characterized by pronounced chorioretinal disease and vitreous opacification, is a less consistent feature of ERU in the USA than in continental Europe.^[1, 2]

Disease Mechanisms:

Although many causes have been postulated, including onchocerciasis, current evidence implicates auto-immunity and leptospiral infection as important factors in the aetiopathogenesis of ERU. *Leptospira* serovars have been detected by culture and by PCR in the aqueous and vitreous of affected horses in both North America and Europe.^[3,4] The predominant isolate identified in ocular fluids of European horses was *L. kirschneri* serovar Grippytyphosa, strain Duyster and it has been postulated that this strain may have an enhanced ability to establish persistent intraocular infections.^[5] Interestingly, this strain is restricted to Western Europe, whereas predominantly serovar Pomona was isolated in North American samples. Whether leptospirosis leads to ocular inflammation as a result of systemic disease, direct effects on ocular tissues of persistent local infections, or by a mechanism involving “molecular mimicry” is unclear.^[6]

Regardless of the cause, ERU is clearly an “auto-aggressive” T-cell mediated disease, associated with CD4+ T-cells and increased transcription of IL-2 and IFN- γ with low IL-4, characteristic of a Th1-like inflammatory response.^[2,7] The role of retinal auto-antigens, including interphotoreceptor retinoid binding protein (IRBP), and to a lesser extent, retinal-S antigen, has been demonstrated in equine experimental models and spontaneous disease.^[8-10] Studies in human autoimmune uveitides have revealed that certain HLA haplotypes are strongly associated with disease. A similar association with ERU was demonstrated with MHC class I haplotype ELA-A9 by serologic haplotyping in German Warmblood horses.^[11] Recent immunogenetic investigations conducted at the University of Minnesota in collaboration with the AHT in Newmarket, suggest that a susceptibility allele for ERU in Appaloosas exists in the MHC region located on Chromosome 20. This could account for enhanced presentation of self-antigens in affected Appaloosas.^[12]

Anti-inflammatory & Cycloplegic Therapy:

Newer treatment strategies for ERU may reduce our reliance on topical and systemic administration of anti-inflammatory medication. However, conventional symptomatic therapy remains the mainstay of

any treatment strategy as control of active inflammation and prevention of unwanted sequelae, such as synechiae, is necessary prior to surgical intervention. Topical corticosteroids (1% Prednisolone acetate or 0.1% Dexamethasone preparations) require frequent application (at least QID) to control bouts of inflammation. Subconjunctival injection of repositol preparations (such as methylprednisolone or triamcinolone) may ensure delivery of anti-inflammatory medication to the eye should the owner have difficulty in complying with an arduous treatment schedule. The importance of gradually tapering anti-inflammatory therapy, rather than abrupt withdrawal, should be stressed at the outset.

Systemic Flunixin meglumine has unparalleled efficacy in the control of intraocular inflammation and relief of associated pain. Initial doses should be administered intravenously if severe intraocular inflammation is identified in order to quickly achieve high concentrations within the ocular tissues. Subsequently, the drug is usually administered orally. Doses ranging from 0.25 – 1mg/kg (SID-BID) are often administered for longer periods than this drug's licensing indicates. The potential for adverse effects should not be ignored and doses selected on an individual patient basis, ensuring that the owner is fully aware of treatment risks. The oral gastroprotectant, Omeprazole, is recommended in animals that are receiving high doses of Flunixin.

Topical therapy with Atropine also has the potential for adverse effects, on GI motility in particular, and signs of colic may be observed after application of a single drop of a 1% solution to some horses. For this reason, the drug should be used "to effect" whenever possible. Use of a 4% solution is seldom indicated, as in even the most severe cases, concurrent application of 1% Atropine and 10% phenylephrine, administered up to 4 times a day, will result in acceptable mydriasis and cycloplegia.

Reducing Antigenic "Drive":

Intravitreal injection of 4mg of gentamycin appeared to dramatically reduce the incidence of recurrent uveitic episodes, although experience with this treatment in visual eyes was limited. Injections were administered under general anesthesia, 8mm posterior to the limbus at the 12 o'clock position.^[13]

Single port pars plana vitrectomy, in which vitreous is replaced by balanced salt solution containing gentamycin, eliminated recurrent uveitic episodes in the majority of treated eyes over variable follow-up periods.^[14] Although practised for over a decade in continental Europe, vitrectomy has not found favour in the management of ERU in the USA, largely because the high incidence of complications, including cataract development, as well as apparent geographic differences in the spectrum of clinical disease.

Although there are anecdotal reports of the use of leptospiral vaccines in the management of field outbreaks of equine uveitis, use of vaccination in the management of ERU was not supported by a recent study.^[15] Oral administration of doxycycline has also been suggested but was recently shown to have limited intraocular penetration following oral administration of 10mg/kg BID to normal horses.^[16]

Suppressing Autoimmunity:

Cyclosporine (CSA) is an excellent therapeutic choice for the management of T-cell-mediated autoimmunity. However, CSA is unable to penetrate intact cornea or sclera, which limits its applicability as a topical drug in the management of intraocular disease. Systemic administration would be cost-prohibitive in horses and could be associated with adverse effects. Novel drug delivery technologies have therefore been applied to the design of intravitreal and, more recently, suprachoroidal implants capable of slowly releasing cyclosporine over extended time periods. These devices have been subject to rigorous testing in normal horses, in horses with experimental uveitis and in clinical cases of naturally occurring ERU.^[17-19] However, despite encouraging results, placement of an intravitreal CSA implant required microsurgical skills, is invasive, and consequently was associated with a significant risk of peri- and post-operative complications, including intra-vitreous hemorrhage, endophthalmitis, and retinal detachments.^[17, 19]

A 6mm diameter, bio-erodible, matrix reservoir was therefore developed for implantation in the suprachoroidal space. Use of this sustained-release cyclosporine delivery device, implanted under a scleral flap, appears to be a safe and efficacious treatment for the management of chronic severe ERU.^[20] A recent study involved 67 horses, each with documented ERU of >3 months duration, that received CSA suprachoroidal implants at 7 different institutions. Over follow-up periods up to 3 years, more than 90% of treated eyes retained vision at 2 years after implantation. Prior to surgery, affected

horses had documented flare-ups, on average, about once every two months. Reduction in frequency of uveitic episodes was approximately 10-fold in treated eyes. It is noteworthy that loss of vision in treated eyes was associated with pre- or post-operative glaucoma, rather than flare-ups of uveitis.^[21] Suprachoroidal CSA implantation is only recommended for management of ERU in horses with a history of frequent recurrences, that are controlled at the time of implantation. Cyclosporine is only a weak anti-inflammatory and can take more than 1 month to establish therapeutic concentrations within intra-ocular tissues.

References:

1. Dubielzig, R.R., J.A. Render, and R.J. Morreale, *Distinctive morphologic features of the ciliary body in equine recurrent uveitis*. Vet Comp Ophthalmol, 1997. 7(3): p. 163-167.
2. Deeg, C.A., et al., *Immunopathology of recurrent uveitis in spontaneously diseased horses*. Exp Eye Res, 2002. 75(2): p. 127-33.
3. Faber, N.A., et al., *Detection of Leptospira spp. in the aqueous humor of horses with naturally acquired recurrent uveitis*. J Clin Microbiol, 2000. 38(7): p. 2731-3.
4. Wollanke, B., B.W. Rohrbach, and H. Gerhards, *Serum and vitreous humor antibody titers in and isolation of Leptospira interrogans from horses with recurrent uveitis*. J Am Vet Med Assoc, 2001. 219(6): p. 795-800.
5. Hartskeerl, R.A., et al., *Classification of Leptospira from the Eyes of Horses Suffering from Recurrent Uveitis*. Journal of Veterinary Medicine Series B, 2004. 51(3): p. 110-115.
6. Parma, A.E., et al., *Detection of an antigenic protein of Leptospira interrogans which shares epitopes with the equine cornea and lens*. Vet J, 1997. 153(1): p. 75-9.
7. Gilger, B.C., et al., *Characterization of T-lymphocytes in the anterior uvea of eyes with chronic equine recurrent uveitis*. Veterinary Immunology and Immunopathology, 1999. 71: p. 17-28.
8. Deeg, C.A., et al., *Uveitis in horses induced by interphotoreceptor retinoid-binding protein is similar to the spontaneous disease*. Eur J Immunol, 2002. 32(9): p. 2598-606.
9. Deeg, C.A., et al., *Immune responses to retinal autoantigens and peptides in equine recurrent uveitis*. Invest Ophthalmol Vis Sci, 2001. 42(2): p. 393-8.
10. Deeg, C.A., et al., *The uveitogenic potential of retinal S-antigen in horses*. Invest Ophthalmol Vis Sci, 2004. 45(7): p. 2286-2292.
11. Deeg, C.A., et al., *Equine recurrent uveitis is strongly associated with the MHC class I haplotype ELA-A9*. Equine Vet J, 2004. 36(1): p. 73-75.
12. Kaese, H., et al. *ELA microsatellite association with uveitis in the Appaloosa horse*. in *36th Annual Meeting of the American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
13. Pinard, C., et al. *Intravitreal injections of gentamicin for the treatment of Leptospira-associated equine recurrent uveitis*. in *36th Annual Meeting of the American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.
14. Fruhauf, B., et al., *Surgical management of equine recurrent uveitis with single port pars plana vitrectomy*. Veterinary Ophthalmology, 1998. 1: p. 137-151.
15. Rohrbach, B.W., et al., *Effect of vaccination against leptospirosis on the frequency, days to recurrence and progression of disease in horses with equine recurrent uveitis*. Vet Ophthalmol, 2005. 8(3): p. 171-179.

16. Gilmour, M.A., et al., *Ocular penetration of oral doxycycline in the horse*. Vet Ophthalmol, 2005. 8(5): p. 331-335.
17. Gilger, B.C., et al., *Long-term effect on the equine eye of an intravitreal device used for sustained release of cyclosporine A*. Veterinary Ophthalmology, 2000. 3(2/3): p. 105-110.
18. Gilger, B.C., et al., *Effect of an intravitreal cyclosporine implant on experimental uveitis in horses*. Vet Immunol Immunopathol, 2000. 76(3-4): p. 239-55.
19. Gilger, B.C., et al., *Use of an intravitreal sustained-release cyclosporine delivery device for treatment of equine recurrent uveitis*. Am J Vet Res, 2001. 62(12): p. 1892-6.
20. Gilger, B.C. and T. Miller Michau, *Equine recurrent uveitis: new methods of management*. Vet Clin North Amer Equine Pract, 2004. 20: p. 417-427.
21. Gilger, B.C., et al. *A novel biodegradable suprachoroidal cyclosporine ocular implant for equine recurrent uveitis*. in *36th Annual Meeting of the American College of Veterinary Ophthalmologists*. 2005. Nashville, TN.

Abstracts

A Series of Qualitative Tear Deficiency Cases in Beagles

H Ehall

Dept of Veterinary Services, HLS
Huntingdon

Introduction:

A canine patient with a red, irritated eye and ocular discharge with or without corneal disease should undergo a Schirmer Tear Test (STT)¹. A STT reading of 15mm/min or above is generally interpreted as normal tear production and dry eye is therefore not considered the underlying problem for the clinical picture. Ocular surface drying, however, may also result from qualitative tear deficiency. The following is a case report of a group of experimental beagles, which suffered from drug-induced qualitative tear deficiency.

Case report:

An 18-month old beagle, which took part in a 13-week safety study for a potential new medicine (PNM), was presented with signs of ocular discomfort in week 5. On examination, bilateral epiphora with conjunctival hyperaemia and mucoid discharge were noted as well as reddening and swelling of the eyelids. An association with the exposure to the PNM was considered and the eyes were closely monitored. Seven days later, the condition of the eyes was regarded to have deteriorated and the eyes were re-examined. In addition to the already described abnormalities of the eyelids and conjunctivae, corneal oedema with a central corneal ulcer were identified. The STT was 28 mm in both eyes, but it was noted that the blue dye on the paper-strip had not moved significantly. The remainder of the ophthalmic examination was unremarkable. Topical application with chloramphenicol ointment (Chloromycetin®, Forley Ltd, three times daily) was prescribed and the ulcer healed promptly over the next few days. A few days later another two dogs receiving the same dose of the PNM developed very similar clinical signs of blepharoconjunctivitis and epiphora. STT was again above 25mm/min in both dogs. In one of the dogs, the meibomian glands were very prominent with excessive gland secretion. Conjunctival bacteriology swabs revealed a heavy growth of *Pseudomonas aeruginosa* and scanty growth of coagulase-negative *Staphylococcus spp.*, which were sensitive to gentamicin. Both dogs received gentamicin eye-drops (Tiacil®, Virbac Animal Health, three times daily) and ketorolac eye-drops (Acular®, Allergan, twice daily) to control the conjunctivitis and they responded well to the treatment. Systemic antibiotics, enrofloxacin (Baytril®, Bayer, 5mg/kg p.o.) were further prescribed in one of the dogs to control the meibomianitis. As epiphora, increased STT readings and various degrees of blepharoconjunctivitis were present in all the other animals receiving the same dose of the PNM, mucinomimetic tear supplementation (Viscotears®, Dr Mann-Pharma, three times daily) was commenced immediately. All beagles responded well and promptly to the treatment with signs abating totally within 7 days of commencement of lubricant in all at risk dogs. They all remained on Viscotears® and were free of further ocular signs for the rest of the study.

Discussion:

A red irritated eye with corneal disease is very often associated with a dry eye and is generally accepted to warrant a STT. A STT of 15 or below is considered diagnostic of KCS¹. However, STT only measures the aqueous component of the tear film and not the amount of lipid or mucin component produced. STT is therefore unlikely to help in diagnosing qualitative tear deficiency. Nevertheless, it is interesting that the blue dye on the paper strip was noted to hardly move in these cases. This may be either due to the viscous components of the tear film playing an important role as carrier of the dye or due to the more aqueous tears being absorbed faster by the paper. For the same reasons, the increased STT readings in these dogs have to be questioned, although a compensative increase in aqueous tear production would appear logical. Tear break-up time has been found a useful tool to help confirm diagnosis of qualitative tear deficiency² and could have been helpful in this series of cases.

Qualitative tear deficiencies are either due to lipid or mucin abnormalities ³. Pre-ocular mucin deficiencies are usually caused by conjunctival goblet cell atrophy ⁴. Disturbances of the meibomian glands result in abnormal lipid secretion with subsequent disruption of the superficial lipid layer of the tear film ⁵. The exact mechanism of the PNM interfering with the tear film quality has yet to be established. Further investigations, including histology of the meibomian glands and conjunctival goblet cells will follow and will hopefully shed some more light on the pathogenesis of this case.

Ocular changes are not uncommonly recognised as a side effect of new drugs and ophthalmoscopies form part of most toxicological studies for potential new medicines. Sometimes, the nature of the changes will already be known from previously collected data or in-depth knowledge of the effect of the tested molecule. At other times they will be more obscure and as in this case provide a challenge to the veterinarian involved in these investigations. This case of PNM induced qualitative tear film deficiency may also be of interest to the clinical ophthalmologist as a potential unexpected finding in the clinic.

References:

1. Moore C.P.: Diseases and surgery of the lacrimal secretory system. In Gelatt K.N. (ed) *Veterinary Ophthalmology*. 3rd ed. Lippincott Williams & Wilkins, Baltimore, Maryland, 1999, pp 583-607.
2. Moore C.P., Wilsman N.J., Nordheim E.V., Majors L.J., Collier L.I.: Density and distribution of canine conjunctival goblet cells. *Invest Ophthalmol Vis Sci* 1987 (28): 1925-1932.
3. Cullen C.L., Njaa B.L., Grahn B.H.: Ulcerative keratitis associated with qualitative tear film abnormalities in cats. *Vet Ophthalm* 1999 (2): 197-204.
4. Moore C.P., Collier L.L.: Ocular surface disease associated with loss of conjunctival goblet cells in dogs. *J Am Anim Hosp Assoc* 1990 (26):458-465.
5. McCulley J.P., Scialis G.F. Meibomian keratoconjunctivitis. *Am J Ophthalmol* 1977 (84): 788-793.

Ocular penetration associated with dental extraction in the cat: 6 eyes

J. R. B. Mould, Eye Veterinary Clinic, Marlbrook, Leominster, HR6 0PH
F. M. Billson, Veterinary Specialist Centre, Cnr Delhi and Plassey Roads, PO Box 307, North Ryde, NSW 1670, Australia

Introduction

The cat eye is prone to penetrating ocular injuries, most commonly from cat claws, and the penetration site is usually corneal or anterior scleral. The cat has an open orbit, however, with most of the orbital margin consisting of soft tissue making it possible for penetration to occur from other directions. In particular there is only soft tissue continuity between the soft palate and the orbital contents allowing for the possibility of penetration from a ventral direction. Standard veterinary dental texts caution against the danger of dental instruments penetrating the orbit but there are few documented examples of ocular trauma resulting in this way. Ramsey *et al* (1996) describe a dog and a cat which had total hyphaema and orbital cellulitis following dental extraction. There was no response to medical treatment and both eyes were removed. Smith *et al* (2003) reported three cats and two dogs. Two of the feline cases resulted in enucleation; the third had orbital inflammation and secondary uveitis but the eye was not penetrated and was retained. One of the dog cases resulted in enucleation after a period of severe illness with ocular and orbital inflammation and septic shock. The second dog died having suffered brain penetration at the time of the dental.

This report is a retrospective case record study of six enucleation specimens from cats with signs of intraocular inflammation occurring at various intervals following dental treatment. Cases 1 and 2 were included in the report by Smith *et al* (2003).

Results

All eyes had been submitted by clinicians with a special interest in ophthalmology except for Case 3 where the clinician had sought advice from an ophthalmologist who suggested the eye be submitted for pathology. All cats had a history of dental treatment including extraction of upper molar teeth at various intervals prior to onset of clinical signs in the eye. In Case 3 it was reported there was an abscess around the carnassial tooth and the bone was described as abnormal.

Case	Breed	Age in years	Sex	Eye	Time from dental to onset of clinical signs	Time from dental to enucleation
1	DSH	9	MN	Right	3 weeks	4 weeks
2	Somali	9	MN	Left	11 month	12 months
3	DSH	n/a	n/a	Right	2 days	3 weeks
4	Persian	4	FN	Left	5 days	n/a
5	Persian	6	FN	Right	Same day	4 days
6	DSH	5	FN	Left	2 days	14 weeks

DSH = domestic short hair, n/a = not available, MN = male neutered, FN = female neutered

The eyes were oriented and external features recorded. All eyes showed external disturbance near the equator in the 6 o'clock meridian and were opened close to or through this area. In all cases internal examination showed a discontinuity in the eye wall within a narrow zone in the peripheral retina at the ora serrata. In all cases the posterior lens capsule was also ruptured in the mid to ventral area with variable posterior prolapse of lens material, cataract and local inflammation. In four cases the vitreous chamber was reduced in volume. Most cases showed some degree of anterior uveitis varying from mild to severe. Cases 1 to 4 were infected with colonies of Gram +ve cocci within the lens material or the

vitreous. No foreign bodies were found in any of the eyes. No canine eyes were diagnosed with comparable lesions in the same period.

Discussion

All eyes in this series had sustained penetrations ventrally in the 6 o'clock meridian along with posterior lens capsule rupture. The presence of two penetration sites allows the trajectory of the penetrating object to be determined with reasonable accuracy. It is only possible for an object to take this trajectory if the direction of travel is ventral to dorsal and therefore from the mouth via the soft palate unless it travels through bone. In Case 3 the bone quality was considered poor in the region of the carnassial tooth and this may have placed the cat at increased risk of penetration. All cases showed the same pattern of penetration and all had a history of recent dental treatment including molar extraction, except for Case 2 where there was an 11 month interval between dental treatment and the reported onset of clinical signs.

The lack of a bony floor to the orbit leaves the cat vulnerable to ventral orbital penetration by foreign bodies and iatrogenically. This is a particular risk with dental extraction in the cat where there is only a thin rim of alveolar bone surrounding the last upper molar caudally. Good dental technique will minimise the risk. Only steady gentle pressure should be applied with dental elevators avoiding excessive force. The opposite hand can be used to cradle the working surface and act as a "stop" if the instrument should slip (Smith *et al*, 2003). It is difficult to gauge the frequency of the injury described here as there are so few reports of documented cases in the literature. The authors speculate, however, that the number of cases in the literature under-represents the scale of the problem and suggest two possible reasons. Firstly, the connection between the dental treatment and the ocular changes may not be made by the clinician or the owner. Secondly, when such eyes are enucleated they may not be submitted for pathological analysis which would confirm the diagnosis.

This series is of enucleated eyes only and cannot indicate the prognosis for management of eyes which have sustained this injury. Lens rupture, phacoclastic uveitis and intraocular infection are always, however, potentially serious problems and the pathological findings in these eyes showed that the decision to remove the eyes was fully justified in the circumstances.

Acknowledgements

The authors are very grateful to N Wilson, Dr C Heinrich, S Paterson, S Manning, and C Hartley for submitting these specimens and providing valuable information.

References

- Ramsey D. T., Marretta S. M., Hamor R. E., Gerding P. A., Knight B., Johnson J. M. and Bagley L.H. (1996) Ophthalmic manifestations and complications of dental disease in dogs and cats *Journal of the American Animal Hospital Association* 32 215-224
- Smith M. M., Smith E. M., La Croix and Mould J. (2003) Orbital extraction associated with tooth extraction *Journal of Veterinary Dentistry* 20 8-17

Mast Cell Tumour of the Nictitans Conjunctiva Presenting As An Intermittent Exophthalmos

KM. Smith BVetMed CertVOphthal MRCVS and S Murphy BVM&S MRCVS
Centre for Small Animal Studies The Animal Health Trust
Lanwades Park, Kentford, Newmarket, Suffolk, CB8 7UU

Case history: A nine year old female neutered English Bulldog x German Shepherd Dog, was referred to the Animal Health Trust with a 25 month history of intermittent exophthalmos and chemosis of the right eye.

The dog had initially presented to the referring vet with conjunctival hyperaemia, slight exophthalmos, protrusion of the third eyelid and pruritis. Medical treatment in the form of systemic nonsteroidals, broad spectrum antibiotics and topical chloromycetin ointment TID OD had been instituted at the first presentation but produced only marginal amelioration in clinical signs after twelve days. At this stage the dog was referred to an ophthalmologist for a second opinion. A diagnosis of presumed orbital cellulitis was made. Skull radiographs and those of the right upper dental arcade taken at the time had revealed no abnormalities. Treatment was changed to ampicillin, oral and topical steroids; eight weeks after the initial presentation the ocular adnexa appeared normal.

Multiple bouts of exophthalmos and chemosis, occurring with increasing frequency, had been observed by the owner and referring vet since then. Signs had resolved within 48 hours, with or without treatment. The owner felt that clinical signs could be induced by the chewing of bones or hard toys. Four months prior to presentation at the Animal Health Trust, the nictitans gland prolapsed during a bout of exophthalmos and chemosis: subsequently remaining prolapsed even when other signs had disappeared.

On presentation the right eye exhibited a mild conjunctival hyperaemia and the nictitans gland was prolapsed. There was no evidence of exophthalmos and both globes were equally easy to retropulse. No pain was encountered on opening the mouth. The remainder of a full ophthalmic examination was within normal limits bilaterally. General clinical examination revealed no abnormalities, other than obesity. A decision was taken not to investigate the condition until a further episode occurred. The need to replace the third eyelid gland was acknowledged, but it was considered not prudent to do so until the underlying cause had been identified; a further bout of swelling occurring postoperatively could have lead to wound breakdown.

Within 24 hours the owner reported an acute onset of signs, and the dog was re-presented. At this stage ophthalmic examination revealed intense chemosis of the ventral palpebral conjunctiva, protrusion of the third eyelid, and swelling of the prolapsed nictitans gland OD (Fig.1). No obvious exophthalmos was detected, and again both globes were equally easy to retropulse. Differential diagnoses at this stage were allergy, retrobulbar cellulitis/foreign body, arteriovenous shunt, or orbital neoplasia.

Ultrasonography of the orbit revealed no obvious abnormalities. The same day, the dog underwent general anaesthesia and an MRI scan of the orbits was performed (Figs. 2 and 3) This revealed the right globe to be subtly displaced caudally and dorsolaterally by a discrete mass measuring 20mm x 8mm rostral to the cornea, consistent with swelling in or of the third eyelid. On the dorsal plane scan the swelling could be seen to extend medial to the globe. Surgical biopsies were taken from the swollen nictitans gland and from the ventral palpebral conjunctiva and were submitted for histopathology. By the time the MRI scan was complete, there had been significant resolution of the chemosis.

Histopathology of the nictitans gland biopsy subsequently revealed infiltration of the conjunctival stroma and the gland itself by sheets of round cells (Fig 4) (identified by pinacyanol staining as moderately well differentiated mast cells, (Fig. 5)), accompanied by eosinophils. A moderate nuclear atypia was observed. The conjunctival biopsy revealed a lymphoplasmocytic conjunctivitis.

Survey imaging in the form of chest radiographs and ultrasonography of the abdomen revealed no signs of metastasis. Skin lesions were absent and palpation of the lymph nodes was within normal limits.

Fourteen days after the initial presentation the entire third eyelid was excised. Schirmer Tear test (1) readings were recorded as 20mm OS and 21mm OD wetting /minute prior to surgery. The surgical procedure was performed as described by Gelatt (2001) and the excised third eyelid submitted for histopathological evaluation. The conjunctiva was apposed using a continuous inverting suture pattern of 0.7 metric polyglactin (Vicryl, Ethicon). Post – operative treatment consisted of potentiated amoxicillin 20 mg/kg (Synulox, Pfizer) BID per os for 7 days, carprofen 4mg/kg (Rimadyl, Pfizer) BID per os for 5 days, chlorphenamine (Piriton, GlaxoSmithKline) 0.18mg/kg per os for 7 days and topical chloramphenicol ointment (Forley Ltd) BID OD. Histopathology of the entire third eyelid confirmed the presence of mast cell tumour. Neoplastic mast cells were present to the margin of the specimen.

Ten days postoperatively, no further episodes had occurred. Some conjunctival hyperaemia was evident but no chemosis. Snip biopsies of inflamed tissue close to the suture line were taken under local anaesthetic; histologically these exhibited low-grade inflammation, with no evidence of mast cells. Twenty-one weeks follow –up have so far been achieved with no of recrudescence of clinical signs

Discussion: Neoplasms of the conjunctiva reported in veterinary literature include squamous cell carcinoma, fibrosarcoma, papilloma, melanoma, adenoma, lymphoma, haemangioma and haemangiosarcoma. Mast cell tumours of the conjunctiva have rarely been reported (Johnson et al, 1988, Grahn et al 1994) and the author is aware of only one previous report of mast cell tumour of the nictitans conjunctiva (Hallstrom, 1970). Middle- aged dogs (7-10 years) appear predisposed. A protracted history of intermittent clinical signs is a feature of conjunctival mastocytosis, with histories of one year reported by Grahn and others (1994) and several years by Johnson and others, (1988)

The owner's observation that the chewing of bones led to the development of clinical signs can be explained by the increase in intraorbital pressure during chewing causing mast cell degranulation. This phenomenon is known as Darier's sign (Tams and Macey, 1981).

Although the referring vet reported exophthalmos as a clinical sign, this was not a feature of the disease when the animal presented to the AHT. This is likely to be related to the relative position of the nictitans gland: the prolapsed gland having a tendency to push the globe caudally when a bout of inflammation occurred.

Mast cell tumours are predominantly a cutaneous neoplasia although they have been reported in several mucosal sites. In the case described, the pathologist reported the tumour as moderately well-differentiated. The mast cell grading systems devised by Bostock (1973) and Patnaik and others (1984) include criteria related to invasiveness, which cannot be applied to non-dermal tissue. This means that mast cell tumours of the conjunctiva may have different biological behaviour and that grading them, as a means of assessing prognosis, may not be useful.

In this case 'dirty' margins were present post- surgery. There is some debate as to whether complete surgical margins are a necessary prerequisite for a successful outcome when removing well- or moderately- differentiated mast cell tumours (Misdorp, 1987 and Murphy and others, 2004). The decision to treat by conservative surgical excision alone, rather than to use adjuvant treatment (e.g. wide local excision, which would have involved enucleation, chemotherapy or radiotherapy) was based on the relatively benign behaviour of other cases of conjunctival mast cell tumour seen at the AHT (Murphy, 2005), the dog's obesity (hence the wish to avoid systemic prednisolone) and the fact that the opportunity for treating the site more aggressively in the future has not been lost.

Removal of the nictitans gland can significantly reduce tear production (Helper and others, 1974) hence the need for pre- and post- operative monitoring . Thus far, STT (1) values appear unaffected.

References:

Gelatt K.N. (2001) Surgical procedures for the conjunctiva and nictitating membrane. In: Small Animal Ophthalmic Surgery, Butterworth Heinemann. Pp176-178

Johnson B.W., Brightman A.H. and Whiteley H.E. (1988) Conjunctival mast cell tumor in two dogs. JAAHA 24: 439-442

Grahn B., Wolfer J. and Randall J. (1994) Diagnostic ophthalmology. Canadian Vet. Journal 35: 730-731

Hallstrom M. (1970) Mastocytoma in the third eyelid of a dog. JSAP 11: 469-472

Tams D. and Macy D. (1981) Canine mast cell tumours. Comp. Cont. Ed. Prac. Vet. 3: 869-876.

Bostock D.E. (1973) The prognosis following surgical removal of mastocytomas in dogs. JSAP 14: 27-40

Patnaik A.K., Ehler W.J. and MacEwan E.G.(1984) Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. Vet. Path. 21: 469-474

Misdorp W. (1987) Incomplete surgery, local immunostimulation, and recurrence of some tumour types in dogs and cats. Vet. Quarterly 9: 279-286

Murphy S., Sparkes A.H., Smith K.C., Blunden A.S., and Brearley M.J. (2004) Relationships between the histological grade of cutaneous mast cell tumours in dogs, their survival and the efficacy of surgical resection. Veterinary Record 154: 743-746

Murphy S. (2005) Personal communication.

Helper L. C., Magrane W. G., Koehm J., and Johnson R. (1974) Surgical induction of keratoconjunctivitis sicca in the dog. JAVMA 165: 172-174

Figure 1 Right eye- appearance at re-presentation



Figure 2 MRI- dorsal plane scan

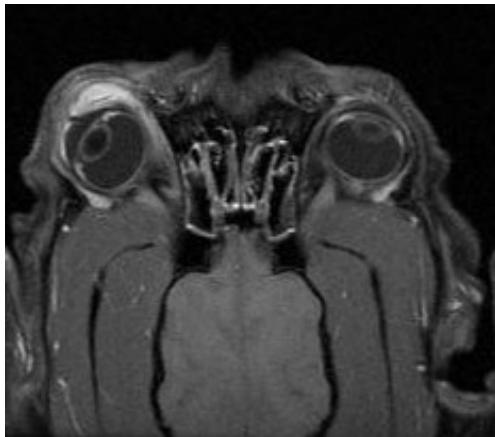


Figure 3 MRI-transverse plane scan

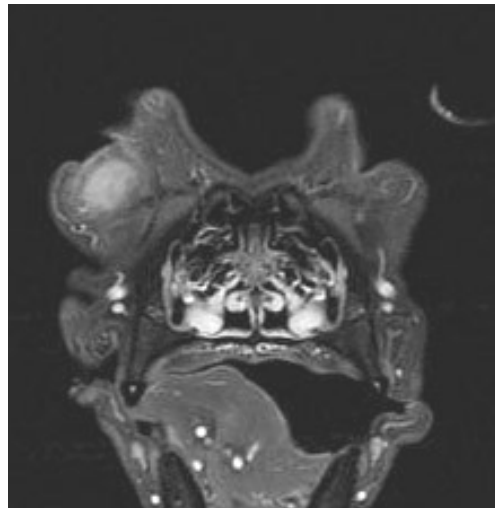


Figure 4 Nictitans gland biopsy H&E stain

Figure5 Pinacyanol stain

Myopia in three dogs associated with early compromise in visual experience.

DL Williams MA VetMB CertVOphthal MRCVS

Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge
CB3 0ES

Introduction

It has previously been reported that the majority of dogs appear emmetropic or very slightly hypermetropic (-0.3 ± 1.4 D relative to infinity) while the German Shepherd, Rottweiler, and Miniature Schnauzer breeds have an increased prevalence of myopia.(1) The Labrador retriever has been noted in a further study by the same group to have myopia associated with elongation of the vitreous body.(2) We might suppose from these findings that canine myopia is a heritable defect. Yet in man the interaction between genetic traits and the environment is complex. (3) Near work in childhood is acknowledged to have a powerful effect on the development of myopia and this association is underlined by animal models in which individuals of a number of species, reared with minus lenses in place and thus focussing abnormally close, develop myopia. (4) This association has not previously been reported in the dog. Here we report three dogs with severe compromise of visual experience in development associated with myopia in later life.

Material and methods

Three dogs were referred with apparent visual dysfunction but apparently normal ophthalmic findings. Routine ocular examination with direct and indirect ophthalmoscopy and slit lamp biomicroscopy was followed by streak retinoscopy using a Welch Allyn retinoscope and lenses arranged in a ret bar, performed after mydriasis and cycloplegia with topical tropicamide as previously described.(5)

Case reports

The first case where an association between early compromise in visual experience and later myopia was postulated was that of a 3 year old Yorkshire terrier with a history of having been reared for the first year of its life in a tea chest. Behavioural abnormalities suggested defective vision although there were no obvious ocular defects on routine ophthalmoscopy. Visualisation of the retina by direct funduscopy was most clearly made at a setting of -5 D and thus retinoscopy was attempted. While difficult because of the temperament of the dog, retinoscopy showed a refraction of -4.5 - 5.0 D.

The other two cases were greyhounds in a re-homing shelter having failed as racing animals. The animals were four and five years old at time of examination. Both had a history of being reared in a small kennel with limited access to open areas. They did not show obvious signs of defective vision although having not been handled, were naturally somewhat boisterous. Retinoscopy demonstrated both dogs to be myopic by -3.5 D. No other ocular abnormalities were noted.

Discussion

These three dogs illustrate a number of points of importance to veterinary ophthalmologists. First is the importance of including retinoscopy in our armamentarium of diagnostic tools. The first books on the subject such as *Veterinary Ophthalmology* by Nicholas (translated by Henry Gray 1914) devoted a considerable proportion of their discussion to the use of retinoscopy for refraction, yet from then until the most recent edition of Gelatt's *Veterinary Ophthalmology* the subject was almost entirely omitted. Dogs with defective vision (manifest mainly as behavioural problems) for which no ocular defects are noted on routine ophthalmoscopy, should be subject to retinoscopy.

Second this is, to the author's knowledge, the first report of myopia associated with defective early visual experience in a companion animal. The condition is widely recognised in children – indeed there

appears to be an epidemic of juvenile myopia in the Far East associated with excessive reading and school work in young children. (6) Experimental animal models of myopia have been used widely since Hubert and Weissel first showed an association between early visual deprivation and changes in vision. The finding of myopia in two gaze hounds is particularly interesting as these animals might be presumed to be particularly likely to be emmetropic given the ecology of the hunting niche they occupy.

It is to be regretted that ultrasonographic biometry of the globes in these dogs was not possible, since it is an abnormality in axial length that confers myopia on children with excess near work (7) and in the Labrador retrievers investigated by Murphy and co-workers. (2) It might be supposed that myopia in the three dogs reported in the current presentation would also be associated with an increased globe axial length – further work in this area would be worthwhile.

While in man high myopes (those with a refraction greater than $-5D$) also have ocular abnormalities such as cataract, glaucoma, myopic tilted optic discs, lacquer cracks and retinal detachment, (8) individuals with the degree of myopia noted in these three dogs are unlikely to be affected by associated ophthalmic defects. Thus it is not unusual to find these dogs having an ametropia which is not evident until retinoscopic refraction is undertaken.

A final thought concerns the possible number of dogs with behavioural abnormalities which might be attributed to an undetected ametropia in these animals. Since veterinary ophthalmologists, at least in the UK, appear not to be regularly refracting their patients at present, we may be missing a number of dogs with behavioural defects which could be attributed to an abnormality of refraction in an otherwise normal eye.

References

- (1) Murphy CJ, Zadnik K, Mannis MJ (1992) Myopia and refractive error in dogs. *Investigative Ophthalmology and Visual Science* 33:2459-63.
 - (2) Mutti DO, Zadnik K, Murphy CJ (1999) Naturally occurring vitreous chamber-based myopia in the Labrador retriever. *Investigative Ophthalmology and Visual Science* 40:1577-84
 - (3) Feldkammer M, Schaffel F (2003) Interactions of genes and environment in myopia. *Developments in Ophthalmology* 37:34-49
 - (4) Yinon U (1984) Myopia induction in animals following alteration of the visual input during development: a review. *Current Eye Research* 3:677-90
 - (5) Davidson MG (1997) Clinical retinoscopy for the veterinary ophthalmologists. *Veterinary and Comparative Ophthalmology* 7:128-137
 - (6) Saw SM, Tong L, Chua WH, Chia KS, Koh D, Tan DT, Katz J (2005) Incidence and progression of myopia in Singaporean school children. *Investigative Ophthalmology and Visual Science* 46:51-7
 - (7) Morgan IG (2003) The biological basis of myopic refractive error. *Clinical and Experimental Optometry* 86:276-88
 - (8) Saw SM, Gazzard G, Shih-Yen EC, Chua WH (2005) Myopia and associated pathological complications. *Ophthalmic and Physiological Optics* 2005 25:381-91
-

The Retrobulbar Space

Another magnificent weekend of presentations I'm sure you'll agree. I do hope Gill has managed to keep her voice with the amount of talking we've made her do. Knowing Gill she will have had to keep herself well lubricated to keep going! Great to have Derek Knottenbelt with us too- many thanks to him and to David Gartry into the bargain. Great appreciation of our sponsors of course and especially to VetXX for funding the proceedings which seem to get bigger and bigger each year!

David Williams
