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Brachycephaly related diseases and the eye - BOS syndrome

The purpose of these talks is to raise awareness of the direct and indirect problems and risks of a brachycephalic conformation in companion animals. Some of the ocular diseases that affect brachycephalics and are covered here are not necessarily due to brachycephaly, but either develop more frequently because of brachycephaly or have a worse prognosis due to it. Therefore, the talks will cover the anatomy and physiology of the brachycephalic cornea and eyelid, and how the eyelids, tear film and cornea can be affected directly or indirectly by brachycephaly.

Brachycephalics dogs and cats share a number of characteristics that pose a special ocular challenge in the face of ocular disease. Although the eyes of brachycephalics appear to be large they are not. The eyes appear to be large due to a mixture of factors including comparatively much smaller (anterior) skull structures, very shallow sockets and a wide interpalpebral fissure (a wider-than-usual space between the upper and the lower eyelid). This situates the globe in a relatively anterior position with respect to the orbital rim in comparison to other skull conformations. Unfortunately, these conformational characteristics mean there is a potential over-exposure of the surfaces of the conjunctiva and cornea. To make matters worse, the corneas of brachycephalic dogs and cats contain a lesser number of nerve trunks that carry sensory information to the brain (eg. Ophthalmic branch of the Trigeminal nerve, CN V).

Last but not least, the additional morphological effect of very short noses is that the medial canthus is “tucked-in”. In Pugs, specifically, this makes the medial canthus be deeply positioned relative to the rest of the facial skin (i.e., the skin is pull inward in the medial canthus) and the medial corner of the eye is not lined with conjunctiva but with skin that contains hairs. When the eye rotates medially, the medial bulbar conjunctiva and cornea rub against the skin hairs, irritating them. In addition, the medial lower eyelid (and sometimes the medial upper eyelid) of brachycephalics develop entropion, aggravating the ocular surface irritation. Last but not least, Brachycephalics with a prominent nasal fold may also have nasal fold trichiasis.

All in all, this undesirable conglomerate of craniofacial/periocular/adnexal characteristics constitutes a poor design for ocular health. This is especially important when surface ocular disease develops.

The tear film is a delicate and intricate set of superimposed layers. The average amount of blinks per minute is determined by the ability of the tear film to maintain its complex structure without breaking down. The moment it breaks down the cornea feels this, the eyelids blink and more tears are produced. Corneal sensation plays an important role in this. The relative reduction of corneal sensation demonstrated in brachycephalics is counterproductive. In addition, a large interpalpebral fissure makes the distribution of the tear film more challenging, while the central cornea can easily develop early tear film break-up with localized dryness between blinks.

Some brachycephalics can develop problems due to this, such as Pigmentary Keratitis of Pugs (i.e., progressive pigment deposition) and central corneal ulcerative disease. Brachycephalics have a general predisposition to corneal ulcerative disease and dry eye (the latter also predisposes to corneal ulcerative disease in brachycephalics and Spaniel breeds).

Entropion in brachycephalics, as mentioned earlier, usually occurs in the medial lower eyelid and in the case of Pugs also affects the medial canthus. In felines, brachycephalia is often seen in association with lower medial eyelid entropion. Unfortunately, this type of entropion is difficult to visualize because. However, one must realize that in these cases these hairs rub the medial-to-central cornea of each eye every time one of the eyes rotates medially. This happens several hundred times a day, every day, and so a relatively imperceptible medial entropion of the lower eyelid can become an important source of irritation. It is likely that this physical disruption also has a negative effect on tear film stability.

One eyelid problem of concern in some brachycephalics, particularly English Bulldogs, is the development of central upper eyelid ectopic cilium. It can happen in other breeds too but Bulldogs seem predisposed. It is always worth examining the conjunctival surface of the central upper eyelid for ectopic cilium in young Bulldogs with ulcerative disease, in addition to first measuring tear production (STT-1) and also ruling out the presence of foreign bodies from the conjunctival sacs an underneath the third eyelid. Ectopic cilia occur in other dogs too brachycephalics, there is a worry that it can lead to rapidly deteriorating corneal disease and it requires our rapid attention. Distichiasis that are short and stiff can also be a problem in the some brachycephalic breeds and be associated with keratitis, which is sometimes ulcerative.

Pigmentary Keratitis, also previously described as Pigmentary keratopathy, is a relatively prominent and rather frequent condition of the cornea of Pugs that may lead to blindness

in advanced cases. This author has observed pigment is often present in the limbus of most Pugs, even in those that are only a few weeks old, and there is often more pigment medially, and laterally, than in any other part of the limbal circumference. Pigment proliferation usually starts in the medial limbus where there is medial canthal and lower eyelid entropion. It progresses onto the central cornea in a triangular "piece of pie"-shape (the apex pointing towards the pupil). As the proliferation progresses the pie-shape rounds off and widens at the tip, covering the medial pupil and ultimately the entire pupil. Occasionally, pigment proliferates from the lateral limbus and joins the first proliferative pigment plaque centrally. Vascularization soon ensues. This author has also observed that in cases with vascularization the pigment is often found not only in the epithelium but also in the superficial stroma. This is not surprising, as vascularization and deeper pigmentation are signs of chronic corneal irritation and this is appears to be a chronic corneal problem caused by low to medium grade, persisting ocular surface irritation. A population study of Pugs in the US suggested that entropion and macropalpebral fissure were not factors that determine the development of pigment in Pugs. However, another population study that was just concluded in the UK found, for the first time that entropion is positively associated with the development of pigmentary keratitis in Pugs (personal communication – Maini S *et al* study 2018). The results of this interesting and most revealing study will hopefully be published soon.

The cause of Pigmentary Keratitis (i.e., progressive corneal pigmentation) in Pugs has been described to be closely associated with the presence of medial lower eyelid entropion. The severity of the entropion is linked to the severity of the pigmentary keratitis, which worsens with age (i.e., over time). Recent microscopy studies have shown that this is an inflammatory condition. Not surprisingly, there are reports that associate the reduction of corneal pigment in Pugs after medial canthal surgery (i.e., medial canthoplasty) that also reduces the macropalpebral fissure. This is often supported by medical therapy such as the use of topical cyclosporin and preservative-free, artificial tears.

While superficial keratectomy may be used to remove pigment from a cornea it may be deep and it may grow back quickly. There is no fail-proof method to remove corneal pigment though some studies have investigated keratectomy plus eyelid surgery, or cryotheraphy plus eyelid surgery, in addition to a variety of topical medications.

Primary dryness is not commonly a factor of PK in Pugs, but it must always be considered a potential problem that can worsen the presentation.

The author has been treating Pugs over some years with a varied combination of bilateral medial canthoplasty, keratectomy, bandage lens placement, topical preservative free lubrication and/or topical ciclosporin with varied success, in many cases arresting and/or regressing pigment proliferation partially, and in some cases restoring vision.

A recent review of brachycephalic ocular syndrome of dogs suggested there should be a breeding focus on periocular conformation, the reduction of the exaggerated facial features that are associated with poor periocular conformation. This is in line with

breeding practices that increase nose and anterior cranial length in general to improve the severe upper airway issues affecting brachycephalics .

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Eye diseases in cats (I) – sequestrum, FHV1, Eosinophilic keratitis, FABK

Feline corneal sequestrum

Feline corneal sequestrum is typically known as a spontaneous corneal disease of cats. It has also been described in a dog and in horses. The nature of the pigment is not fully known and although it has been reported it could be due to porphyrins, these have been demonstrated to be absent in the tears of cats, and other candidates, such as pigment, are believed to be involved – though this has not been conclusively proven. Seauestra has a tendency to affect brachycephalic cats and a few predisposing factors are known to exist in cats such as breed, entropion, performing a superficial grid scrape (or grid keratotomy) and, generally speaking, repeated trauma. FHV-1 is not conclusively proven to be associated with the development of sequestra, as many cats with sequestra are negative for FHV-1 and not all cats with FHV-1 develop sequestra. It is theorized that even relatively subtle microtrauma, when continued or repeated, might be enough to be associated with the development of sequestrum. A study theorized that an unstable tear film might be a predisposing factor, supposedly due to the microtrauma that it would lead to, although the same authors concluded at a later time that an unstable tear film, as

measured by tear break up time and goblet cell number in a low number of cases (n=11), was not likely to be an important factor in the development of feline corneal sequestra. However, it is important to note that something as subtle as an unstable tear film in a brachycephalic cat, with an inherently less sensitive cornea than a non-brachycephalic cat, might still play a role in a multifactorial pathogenesis, where individual factors are difficult to quantify separately. Regardless of the presence or absence of subtle predisposing factors, it is always important to rule out any known associated problems. It is also important to correct those that are amenable to treatment (ie entropion – even very mild cases of medial lower eyelid entropion).

Feline corneal sequestra require superficial keratectomy. This may be followed by the use of a bandage lens and topical medical and oral therapy. This includes, minimally, a topical antimicrobial until re-epithelialization is achieved and an oral anti-inflammatory. In addition, and depending on surgeon's preference, topical use of serum eyedrops may be added for their generally proven positive effect on reepithelialization and stromal wound stabilization. In addition, soothing, preservative-free, viscous tear-drops may also be used and all entropion, even if mild, should be corrected under the same anesthetic event. Sequestra have a tendency to recur after removal. One study showed a tendency for sequestra to have a lower recurrence rate when vascularization was still present, either through grafts or through persisting corneal vascularization in the absence of a graft. In addition, it showed that the clipping of a conjunctival pedicle graft used post-keratectomy could be associated with a higher recurrence rate. Moreover, a study using corneolimboconjunctival transposition (CLCT), which transposes vascular conjunctiva onto the cornea, showed none of the cases recurred.

When the bed of a stromal defect is at 50% of corneal depth or more, corneal grafting is strongly recommended for corneal repair. A number of techniques are available including the use of conjunctiva (in the form of advancement grafts, pedicle grafts and island grafts in cases where the cornea is already vascularized), the use of biomaterials (porcine intestinal submucosa among others) and CLCT. The latter is a surgical option that avoids the need for donor tissue, the use of any other foreign grafting material and offers the additional advantage of having an inherent ability that the corneal section of a CLCT can regain a significant amount of transparency. This is particularly important for centrally located corneal lesions. As mentioned above, the use of keratectomy followed by CLCT has been proven to work well for the surgical treatment of corneal sequestrum in cats.

Feline Herpes Virus -1 (FHV-1)

Treatment for FHV-1 is a topic of interesting discussion. As the virus is difficult to kill and cats can be difficult to medicate, a number of treatment methods have been advocated for use in veterinary ophthalmology. Most have their basis in the scientific literature available to date, although results are perhaps not always interpreted with the clarity that they deserve. Some of the commonest treatments involve the oral administration of interferons and L-lysine, topical treatment with antivirals and the more recent use of a specific orally administered antiviral (famciclovir).

Interferon (IFN) and L-Lysine have been used in tightly controlled studies, where in most

cases, specific pathogen free cats were medicated pre-infection prior to the experimental inoculation of the virus onto the eye. IFN was shown to decrease the cytopathic effects of the virus although it showed no effects on clinical signs. There is an anectodal report in abstract format of reduced severity of clinical signs. IFN is destroyed by the stomach when administered but it is absorbed/exerts its effect through contact with the mucosa of the oral cavity and esophagus. However, the ability of IFN to achieve an observable, significant effect is questionable. A similar conclusion is reached when reading studies about L-lysine, which should work by reducing the levels of arginine, an essential aminoacid for the cat, and that should lead to interference with viral replication. However, clinical trials show arginine is not reduced through the ingestion of L-lysine. Despite this, some studies suggest there may be a reduction of the amount of viral shedding of FHV-1 in carrier cats, though again, the severity of clinical signs and the rate of recurrence do not seem to be affected.

Antivirals target virus replication, which is why their effect is considered "-static" and not "-cidal", and why they require frequent use if used topically.

The specificity for FHV-1 is not known for all. It is known that TFT and Idoxuridine have specificity for the feline virus in vitro and that it must be used 4-6x day and that at least the latter, unfortunately, has poor tolerance when applied topically. Cidofovir may be applied topically and only 2x day. It has been shown to reduce the severity of clinical signs and shedding.

Penciclovir, Ganciclovir and Acyclovir have not been trialled topically although there is one report that used acyclovir topically and it was reported to be well tolerated. These drugs are toxic to cats' liver, kidney and bone marrow.

The notable exception to this is famciclovir, which has penciclovir as its active metabolite. Studies have shown it must reach a concentration in blood of 3.5µg/mL to be effective in cats. Recommended doses of about 90 mg/kg twice daily are recommended and safe though reports of doses of 62 mg/kg do not reach the blood concentration target but appear to work clinically and may be used for the longer term.

Eosinophilic keratoconjunctivitis (EKC) of cats

EKC in cats is thought to be an immune mediated condition. A connection between FHV-1 and eosinophilic keratitis has also been suggested. The cellular infiltrate is different than the condition seen in dogs with a majority of neutrophils, some lymphocytes and plasma cells, and clusters of eosinophils. Diagnosis is reached when eosinophils are seen on cytology. A thorough and systematic scan of the cytology slide is extremely important or eosinophils may be missed. The lesion is cellular (proliferative) in either multiple, white to pink, slightly elevated spots or a plaque and might up-take fluorescein stain. As in dogs, it has a tendency to appear in the dorsolateral paralimbal cornea and conjunctiva, but it can appear anywhere in the corneal circumference. It is also accompanied by a

vascular response, mucous and discomfort, and it has a tendency to also progress to affect the pupillary axis of the cornea. Diagnosis is as of LPI of dogs.

Treatment consists of the topical application of a corticosteroid, such as dexamethasone phosphate 1% in high frequency doses – very similar to the treatment of LPI in dogs. Some clinicians advocate the topical use of ciclosporin although some cats could find it irritating and will not tolerate it. In cases where the use of a topical corticosteroid may induce re-activation of a latent FHV-1 infection ciclosporin may be the only choice. The concomitant use of Famvir in these particular cases may also be indicated. Historically, systemic megoestrol acetate may prove effective for non-responsive cases although the drug is known to have a significant number of potential side effects. As in LPI in dogs, medication may be slowly tapered to a maintenance dose over a period of two months (e.g. once or twice daily, and occasionally every other day applications).

Feline Acute Bullous Keratopathy

This is a fascinating and rapidly developing corneal disease of cats that can have disastrous consequences for the cornea. The condition remains idiopathic and treatment options have been presented and discussed but have not been thoroughly studied to date. Occasional case series are emerging in the veterinary literature. Algoever I (DipECVO) presented 14 cases at the ECVO annual meeting in Trieste, Italy, in May of 2012. This included 12 unilaterally affected and 2 bilaterally affected cats. Treatment options used varied from keratectomy, conjunctival pedicle grafting, third eyelid flap and/or the oral administration of famcyclovir. There was a reported 22 days until resolution of clinical signs in the cases that responded and two cases affected bilaterally did not respond to surgical or medical + surgical treatment. Eight cases resolved with surgical treatment alone and, interestingly, four cases were reported to have resolved with medical treatment alone. This led the author to conclude that it is possible that cats affected bilaterally might be presenting at a later stage of the disease and that they have a worse prognosis than unilaterally affected cats. More information has become available since and the disease seems to be associated with a break in Descemet's membrane, at least in a number of cases. The cause is not yet clear but treatment with a third eyelid flap, which puts some pressure over the bulla, or keratectomy with reconstruction for more advanced cases, is necessary. Early recognition of the disease and early treatment are paramount.

Eye diseases in cats (II) - uveitis, lens diseases, FDIM, and the glaucomas

There are many causes of uveitis in cats, though it is important to note that up to 75% of uveitis in cats are idiopathic. Common causes include FeLV, FIV and Toxoplasmosis, though there are other possible culprits that may be difficult to identify. The reason such a large percentage of the uveitis in cats are idiopathic may be our inability to find an infectious agent, or it may be, as suspected, that the primary insult (i.e., a possible infection) is no longer present and the recurring or persisting episodes are caused by a non-specific immune mediated response that is triggered by external stimuli or never ceases and persists.

Lens luxation is normally secondary in cats, while it is often primary (hereditary) in dogs. In cats it is commonly secondary to chronic uveitis, but also secondary to cataracts, as cataracts cause chronic uveitis. Ideally, cataract surgery is performed before the cataract has had the chance to cause blindness, before it has caused a significant uveitis or lens luxation. A luxated lens can continue to cause inflammation through the constant contact of the lens with the uvea and cornea. It will also cause corneal endothelial damage and vascularization. Lens luxation has also been described as being inherited in 10 related domestic short-haired cats through an autosomal dominant mode of inheritance in one study (Payen G *et al* 2011).

The glaugomas are subdivided into two major forms, primary glaucoma (hereditary) and secondary glaucoma (non-hereditary). Cats may have both. The inherited form of glaucoma affects the mechanisms of aqueous drainage in both eyes, so both eyes are expected to develop this, while secondary glaucoma is always due to some other process that started first (lens luxation, inflammation, neoplasia). Secondary glaucoma might resolve if the primary problem responds to treatment before it leads to irreversible changes.