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Feline Geriatric Medicine

Mini Series

Session Two: Decreasing odds? Management of co-morbid conditions in geriatric cats

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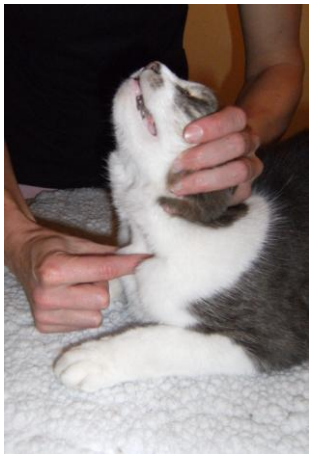

Management of co-morbid conditions in geriatric cats

Common “age-related” diseases that are seen with increasing frequency in an aging cat population include hyperthyroidism, diabetes mellitus, chronic kidney disease (CKD), and degenerative joint disease (DJD). At times, these, and potentially other co-morbid conditions, may require treatment which might be seen as conflicting, or there may be concern that treatment required for one condition is contraindicate in another. However with a good understanding of feline physiology and a sound appreciation of evidence based medicine, we will often be pleasantly surprised at the options open to us.

Treatment of osteoarthritis in a cat with CKD

Both CKD and DJD are seen with some frequency in the elderly feline population. A recent study suggested CKD could be expected in nearly 70% of cats with DJD (Marino et al 2014). Concerns that NSAIDs would be harmful to the kidney, particularly when interstitial nephritis is present, have been allayed by studies which have shown not only do NSAIDs not exacerbate renal dysfunction, but there may even be some renoprotective effects (Gowen et al 2011, Gowen et al 2012). NSAIDs do have the potential to precipitate acute kidney injury (AKI) in cats with CKD, in a dehydrated, hypotensive or hypovolaemic patient. In CKD the kidney has lost its adaptive mechanism to reduced circulating volume as the efferent arteriole is already constricted under the effect of angiotensin II. The afferent arteriole dilates in response to prostaglandins, but NSAIDs inhibit the synthesis of prostaglandin, preventing dilation of the afferent arteriole, leading to reduced renal GFR potentially AKI. In a well hydrated patient even with CKD, good renal perfusion prevents this eventuality but in dehydration, there are no additional measures the glomerulus can take to protect itself against reduced perfusion and AKI may result. For this reason, the use of NSAIDs for DJD at the lowest effective dose can be advocated in cats with stable CKD who are appetent and having no vomiting or diarrhoea, but the drug should be promptly ceased if the patient refuses food or develops gastrointestinal signs. Cats with IRIS stage IV CKD may also be unsuitable candidates for NSAID use as polyuria is likely to be more marked and these cats may struggle to maintain hydration. Alternative treatments for cats that cannot tolerate NSAIDs may include oral buprenorphine, tramadol or gabapentin.

Hyperthyroidism, hypertension, the heart, and the kidneys

In any hyperthyroid cat, thought should be given to the existence of any concurrent medical conditions that the patient may have, as these may influence decisions for management, for example whether general anaesthesia is a reasonable option (for thyroidectomy), or whether significant other disease may influence the patient’s overall prognosis (when considering a definitive treatment). In particular the time of diagnosis of hyperthyroidism is a good time to assess baseline cardiac and renal function, and blood pressure, as hyperthyroidism can significantly affect the renal and cardiovascular systems due to an increase in circulating catecholamines and metabolic rate, and a resultant increase in cardiac output. Restoration of a euthyroid state generally improves the cardiovascular status, but careful reassessment is prudent; possibility of a concurrent primary hypertrophic cardiomyopathy, or hypertension due to some other underlying disease, should not be overlooked. In one study just over 20% of cats went on to develop hypertension despite good control of hyperthyroidism over a 6 month period (Williams et al 2013). The cause of this (eg whether it was related to the appearance of chronic kidney disease) is not clear. This contrasts with an earlier study showing that 87% of hyperthyroid cats were hypertensive, but that adequate control of the hyperthyroidism also controlled the hypertension as far as follow-up was maintained (only over 4 months) (Kobayashi et al 1990).

The identification of co-morbid disease may influence not only the choice and timing of treatment for hyperthyroidism, but may also add some prognostic information. Reduced survival times can be seen in the cats diagnosed as hypertensive as well as hyperthyroid.

With both hyperthyroidism and chronic kidney disease (CKD) occurring with some frequency in the older feline population, it is no surprise that the two conditions are encountered concurrently in a proportion of patients. Studies report anything from 10 to 49% of cats to have evidence of concurrent CKD at the time of diagnosis of their hyperthyroidism. These cats were also consistently identified as having a significantly shorter average lifespan than their non-azotaemic counterparts. This contrasts with the situation of a patient who's mild CKD only becomes apparent after their hyperthyroidism is treated; there is evidence to show that such patients do not have a shortened survival time compared to non-azotaemic well controlled hyperthyroids (eg Williams et al 2010, Daminet et al 2014). This is important given that various studies demonstrate that a large number of cats (between 15 and 50% based on various studies) can be expected to become azotaemic during the first few months after restoration of euthyroidism.

Regardless of the treatment modality used for hyperthyroidism (curative versus control with anti-thyroid medication); if the total T4 falls below the reference range, it is not always necessary to address this, as cats generally do not show any outward signs of hypothyroidism despite a low TT4 (either they are resistant to the effects of hypothyroidism, or, FT4 or T3 are maintained; this has not been well studied). Occasional patients will demonstrate lethargy, inappetence, weight gain or a greasy, scurfy coat, in conjunction with a low TT4, and in these patients the dose of anti-thyroid drugs is best lowered, or, if they have undergone a definitive treatment, levothyroxine supplementation should be instituted. Additionally, where iatrogenic hypothyroidism is caused, if the patient also develops azotaemia, the restoration of a euthyroid state must be the aim, as this is the very subset of individuals that for whom a reduced survival time (around halved) has been demonstrated. In this study T3 levels were not measured in these cats, but cTSH was and was elevated in nearly 70%, implying genuine hypothyroidism rather than non-thyroidal illness (Williams et al 2010). TSH is good way to differentiate between non-thyroidal illness and hypothyroidism as a cause of low TT4, and in cats on long term medical therapy where the combination of azotaemia and hypothyroidism develops unexpectedly, cTSH levels can be helpful to determine whether azotaemia is causing or resulting from a low TT4 (Aldridge et al 2015).

Diabetes and Acromegaly

Acromegaly in the cat is caused by either a functional adenoma, carcinoma, or hyperplasia of the somatotrophin-producing cells in the pars distalis of the pituitary, resulting in excessive growth hormone (GH) production. This stimulates and excessive insulin-like growth factor 1 (IGF-1), mainly within the liver, and typically there is a resultant increase in soft tissue growth, giving large, heavy features (most noticeable in the head and paws) and organomegaly which may be noted on imaging. Consequences of this may include renal insufficiency and cardiac disease, including congestive failure. Arthopathies commonly occur and can be very painful. Neurological effects may be seen if there is pituitary enlargement. Some of the main clinical effects though, tend to be due to insulin-antagonism by GH. Where acromegaly was traditionally considered (very) rare, studies carried out more recently at the RVC (Neissen et al 2015) , prospectively screening all diabetic cats identified acromegaly in nearly one quarter of patients. Many cats lacked what was once considered the "typical" broad faced, large pawed phenotype. When faced with a diabetic cat which is poorly controlled yet *gaining* weight, acromegaly should be considered. Also, there is typically profound polyphagia with acromegaly – more marked that is seen in a typical uncontrolled diabetic, and this sign should also prompt a search for the condition.

Acromegaly should also be considered as a differential diagnosis in any cat where insulin resistance has been confirmed. The condition seems to be more common than hyperadrenocorticism as a cause of insulin resistance, and frustratingly the two conditions can be difficult to differentiate given the tendency for acromegaly to cause adrenomegaly, the high rate of false positive tests for HAC in a patient with non-adrenal but stressful disease, and the fact that both conditions tend to result from a pituitary lesion.

Well validated feline GH assays are generally not readily available in the UK. Serum IGF-1 measurements are used to raise or lower the suspicion of acromegaly. This hormone is more easily measured, and also tends to be more consistently raised in acromegalic cats, as GH release is pulsetile. False-positive results can occur however, in non-acromegalic insulin-resistant diabetic cats. Also, in all non-treated diabetic cats, IGF-1 concentrations are suppressed as a "permissive" effect of insulin within the liver is lacking. As treatment is commenced, IGF-1 levels rise and in fact in long-term treated diabetic cats, may become markedly elevated, even in non-acromegalic subjects (reasons unclear). This demonstrates that the timing of IGF-1 measurement in relation to a diabetic cat's treatment regime must be taken into consideration when reviewing the result (Starkey et al 2004).

Advanced imaging can be helpful in the diagnosis of acromegaly. Not all cats will demonstrate a grossly visible lesion in the pituitary, however, the combination of raised IGF-1 and a pituitary mass would be essentially diagnostic for acromegaly. Also, treatment options are widened if a pituitary lesion is demonstrated.

Reported treatments for acromegaly in the cat include cobalt 60 irradiation of confirmed pituitary tumours, external beam radiotherapy, hypophysectomy, somatostatin and somatostatin analogues, L-deprenyl, bromocriptine and cabergoline.

Pituitary irradiation seems to have some effect in reducing growth hormone concentrations, either transiently or long term; sometimes the effect is delayed. Some relatively long survival rates (over a year) are reported with pituitary irradiation, however, it is not uncommon to see only a temporary benefit to the clinical signs. Historically, somatostatin and L-deprenyl appear to have little or no efficacy. However the RVC has been undertaking a trial using a long-acting somatostatin, and has also recently reported fairly promising results of a trial using long acting injections of the somatostatin pasireotide, although the drug is extremely expensive and side effects (usually diarrhoea) are not uncommon (Gostelow et al 2017). Bromocriptine can be associated with vomiting, which can be severe enough to necessitate withdrawal of the drug. Cabergoline can be used as an alternative, and is better tolerated, and for this reason may be advisable as first line medical treatment. It has not shown a lot of promise in terms of efficacy, however, its effects seem to be dose related and the optimum dose rate has not yet been established. Anecdotally, the drug seems to be effective in only certain individuals, and it is possible that this relates to differing receptor expressions in the tumour.

Where surgery is successful, hypophysectomy could be considered a treatment of choice given it offers a permanent cure, avoiding the possibilities of partial remission or remission followed by relapse which can occur following radiotherapy. Additionally, it is the only treatment that effectively reverses cardiac remodelling and other organ alterations (Borgeat et al 2018). The procedure must considered as higher risk, but with the potential for higher gain. Perioperative mortality rates are high, usually due to blood loss. However it does seem that this risk may be proportional to the size of the tumour and can therefore be better assessed on an individual basis. Of the patients that survive, diabetic remission is frequent, but not a given, although reduced insulin doses and better control should be expected in all cats. There is inevitably a requirement for hormone supplementation post-operatively. Levothyroxine and hydrocortisone must be administered daily lifelong. DDAVP is usually only required short term, as the anterior pituitary can be spared.

The majority of acromegalic cats are diabetic, and adequate management of diabetes mellitus can usually be achieved simply by using greatly increased insulin doses, without any additional treatment for the pituitary tumour. However, this does not improve the profound polyphagia which can be distressing to patient an owner alike, and supportive care for congestive failure and arthropathies may be required. Without definitive treatment, most cats are euthanased because of intractable joint pain or cardiac complications.

References and Further reading

Recent chapters in August's Consultations in Feline Medicine (Volume 7) are particularly helpful for a full discussion of hyperthyroidism, concurrent renal disease, and iatrogenic hypothyroidism.

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