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Endocrinology Case Challenges Mini Series

Session Three: Thyroid Disease

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Hyperthyroidism in cats

Introduction

Hyperthyroidism is the commonest endocrinopathy of cats, typically diagnosed in cats greater than 7 years old. It is generally caused by hyperplastic thyroid tissue or a thyroid adenoma, although malignant carcinomas account for 2-3% of cases. It is more common in some countries than others, leading to a thought that there may be dietary or environmental factors that influence its development but the nature of these is controversial.

Presentation

The most common signs of hyperthyroidism include polyphagia and weight loss. Problems such a manic behaviour were once reported to be common but are less commonly reported now, perhaps because the disease is identified earlier. A summary of the clinical signs attributable to hyperthyroidism and their prevalence is as below.

Feature	*% cats*
Weight loss	87
Palpable goitre	83
Polyphagia	49
Hyperactivity	31
Tachycardia	42
PU/PD	36
Vomiting	44
Cardiac murmur	54
Diarrhoea	15
Muscle weakness	12
CHF	2
Increased nail growth	6
Dyspnoea	10
Alopecia	3
Ventriflexion neck	1
Increased faecal volume	8
Anorexia	7
Panting	9

Of note, a goitre (enlarged thyroid) can be detected in 83% of cases but not all of them. In others, it is thought that the overactive tissue is ectopic, within the thorax, and hence not amenable to palpation. The presence of a goitre is not thought to be specific for hyperthyroidism. Perhaps because the tissue is sometimes inactive, perhaps because other tissue is palpated instead or it may simply be that some cases are not recognised as hyperthyroid if the increases in T4 are early and subtle.

Diagnosis

Clinical signs of hyperthyroidism and an appropriate signalment are quite suspicious of the disease but the diagnosis should be confirmed as several differential diagnoses exist. Diabetes mellitus may cause PU/PD, polyphagia and weight loss. Renal disease may cause PU/PD and weight loss. Gastrointestinal disease or some neoplasias may cause polyphagia and weight loss. Exclusion of these other conditions helps to some degree but specific testing is also advised.

Total T4

In the majority of cases total T4 (tT4) measurement is sufficient for diagnosis, being both highly sensitive and specific for hyperthyroidism. There are numerous different assays available to measure T4, however, and some differences exist between methods. The radioimmunoassay and chemiluminescent assays are generally utilised by larger commercial labs and are considered the gold standard. A point of care ELISA is available but this is less precise and generally overestimates T4 levels and an enzyme immunoassay is available which tends to underestimate T4 levels. Similar to dogs, total T4 can decrease with age and with other diseases and so if a cat suffers from another illness or is older then a T4 in the upper part of the reference range (generally >30nmol/L) MAY be consistent with hyperthyroidism and it should be rechecked at a a later date or further investigated by another method (see below).

Free T4

Free T4 (fT4) can be measured at labs by numerous methodologies with equilibrium dialysis (fT4ed) generally considered to be the gold standard. It is more sensitive than tT4, meaning that those cases with genuine hyperthyoirdism but a tT4 in the upper reference range typically have an elevated fT4 and this can be used to confirm the diagnosis. fT4 is less specific than tT4 and it may be levated in association with numerous diseases. As such, fT4 should not be used on its own to diagnose hyperthyroidism but rather used with tT4 and clinical signs to confirm a diagnosis.

T3 Stimulation test

Hyperthyroidism is generally associated with autonomous secretion of T4 which is not subject to negative feedback. By contrast normal thyroid tissue should be suppressed by T3 or T4. The T3 stimulation test is performed by measuring T4, administering oral T3 for 3 days and then re-measuring T4 to see if it is suppressed, indicated normal thyroid function, or continually excreted. T3 is usually measured at the same time to ensure that the pills were appropriately ingested. While very reliable, the test is typically no longer performed as it is expensive and relatively cumbersome compared to more widely used methods such as fT4.

Thyroid Stimulating Hormone (TSH)

Feline TSH (fTSH) cannot be commercially measured but there is some cross reactivity with the canine TSH (cTSH) assay. In hyperthyroidism then TSH should be suppressed and is typically below the limit of detection whereas it can be measured in cats with normal thyroid function. Unfortunately, the cTSH assay is not sensitive enough to detect normal fTSH levels in a lot of cases meaning that low cTSH is seen in hyperthyoird cats and a lot of euthyroid cats. Normal cTSH concentrations do, however, exclude hyperthyroidism.

Thyroid scintigraphy

Thyroid scintigraphy is highly accurate for the diagnosis of hyperthyroidism. Additionally, it can be used to determine the position of overactive thyroid tissue and therefore determine if surgery is likely to be successful or if ectopic tissue is present and it can give an indication of the likelihood of malignancy. Scintigraphy is rarely performed due to its cost, limited availability, health and safety concerns and the fact that cats need to be isolated for 24 hours after the procedure at a minimum due to their radioactivity.

Ancillary testing

In any cat with hyperthyroidism a blood pressure measurement should be taken as hypertension is a common comorbidity. This should also be checked following successful treatment as it is known to develop even following successful treatment in a number of cases. Urinalysis should also be checked as infections may be present in up to 9% of newly diagnosed hyperthyroid cats. Additionally proteinuria is thought to have some prognostic significance, although even those with proteinuria typically live for several years so the benefit of this measurement is questionable.

Treatment

Having achieved a diagnosis of hyperthyroidism, numerous treatment options exist. These can be divided into continuous therapies (medication/diet) or curative therapies (surgery/radiation). Typically short term management is used in the first instance to stabilise patients and assess their renal function. These treatments are suitable for lifelong therapy but are less cost effective and have a poorer long term outcome compared to then moving on to a definitive treatment.

Medical management

There are 2 licensed anti-thyroidal drugs for use in cats (methimazole and carbimazole). Methimazole is the shorter acting compound and typically needs to be given twice daily whereas carbimazole is given once daily. Carbimazole is metabolized to methimazole in vivo and aside from the dosing regimen, their characteristics (including side effects) are broadly the same. They are available as tablets, oral liquids and a gel that can be applied topically to the pinnae and all forms are thought to be effective although their dosing may not be equivalent. Side effects are seen in a number of cats with anti-thyroidal drugs and they can be broadly be divided into minor, transient side effects and those that form a contraindication to continued treatment with the drug class.

Gastrointestinal signs (vomiting, diarrhoea, decreased appetite, lethargy) are typically mild and dose dependent, improving after 1-2 weeks of therapy and they can be managed through a temporary dose reduction after starting the drugs. Non-dose dependent side effects include facial puritus/excoriations, which can be severe or neutropenia/thrombocytopenia/anaemia, which is typically reversible if identified and the drug discontinued. Rarer side effects include hepatotoxicity, coagulopathy or lymphadenopathy. Heaptopathies can be challenging to spot as ALT elevations are common prior to treatment of hyperthyroidism and are typically expected to normalise with treatment but if other liver enzymes elevate or ALT worsens/fails to normalise this can be a concerning finding. In light of the above, haematologies and liver enzymes should be periodically checked in patients receiving these drugs.

Monitoring response to treatment

In addition to monitoring for the above side effects, any treatment of hyperthyroidism needs monitoring to assess its effects. This primarily consists of measuring total T4, with a target of the lower third of the reference range, and clinical signs, in particular weight.

Renal parameters are also typically monitored as hyperthyroidism is associated with an artificial increase in glomerular filtration rate (GFR), which normalises with successful treatment. The drop in GFR can lead to the development or worsening of azotaemia, which is not novel kidney disease but the unmasking of disease that was previously present, perhaps caused/worsened by the hyperthyroidism. In most instances where chronic kindey disease (CKD) does become apparent after treatment then the restoration of euthyroidism is associated with a 1 stage increase as per the IRIS CKD scheme. This is not a problem for cats with a creatinine initially below 140μmol/L as they are likely to have IRIS stage II disease at worst, which can be successfully managed for several years. In these cases, the hyperthyroidism should be treated as normal and subsequent CKD managed as per IRIS guidelines.

In cats with higher initial creatinine values they may progress to IRIS stage III or IV with treatment. This is associated with a worse long term outcome but also these later stages and worsened azotaemia may be associated with an unacceptable drop in appetite or other signs of CKD. In such instances the need for good thyroid control needs to be balanced with the need for good appetite and continued quality of life, although ultimately any compromise reached is likely to be associated with a relatively short life expectancy due to the inevitable progression of both problems.

Dietary management

An iodine restricted diet (Hills y/d) is available for the treatment of hyperthyroid cats and data is now available that indicates it is generally successful, reducing T4 concentration into the normal range in the majority of cats within the first few months of treatment. Problems can occur with the diet if it is not eaten by cats or other cats are present in the house, as it is not suitable for thyroid cats.

Additionally, if the cat gets any additional food (in the house or by scavenging) then this will negate the effects of the iodine restriction. A longer-term follow-up study was recently published and this indicated that he majority of cats fed the diet exclusively did have normalisation of their T4 but normalisation of weight and heart rate was not as apparent as in cats treated by other methods, bringing the befit of the diet into question, when compared to other methods of treatment.

Surgical thyroidectomy

Hyperthyroidism is associated with focally abnormal tissue and so it is amenable to treatment by resection. This treatment can be very successful but surgeons and owners should be aware that there can be overactive tissue in the grossly normal thyroid gland as well as any enlarged nodules, meaning that bilateral surgery is often required (but this can be staged). Additionally, up to 20% of cases have overactive tissue located within the thorax, which is not surgically accessible. Scintigraphy can help to identify the location of abnormal tissue prior to surgery.

Bilateral thyroidectomy runs the risk of causing iatrogenic hypoparathyroidism if the parathyroid glands are not successfully identified and preserved and so this should be monitored for and treated as indicated below.

Radioiodine treatment

Radioiodine therapy is considered by most to be the gold standard therapy. This involves giving a single subcutaneous injection of I^{131} to the patient which is taken up by the overactive thyroid tissue. The I^{131} emits beta particles which are highly damaging within 2mm of their location, meaning that the drug will effectively target and destroy overactive thyroid tissue, regardless of its location. A single treatment is around 95% effective, with a further 2-3% responding to a second treatment. In the remaining 2-3% the cause of treatment failure is a thyroid carcinoma and in such cases they can respond to treatment but higher doses are required, which can only be administered at Bristol and Glasgow Universities within the UK.

Although it is the gold standard, several problems potentially exist with this treatment. It is only available at limited sites and there is usually a waiting list. The up-front cost is high but this is mitigated by the absence of long term medication/monitoring needs. The largest problem is that the cats are radioactive following injection and therefore need to be quarantined for 1-3 weeks, depending on the dose given and the local rules. During that time handling is limited and this can be distressing for cats/owners but more importantly can limit the ability to treat comorbidities during that time. Given that a heart murmur is present in upto 50% of cats with hyperthyroidism and cardiac hypertrophy, potentially leading to heart failure, is a consequence of hyperthyroidism then this is a significant concern in these cats. Additionally, thyroid medication must be stopped prior to treatment to ensure the thyroid gland is sufficiently active for the treatment to work. The combination of cardiac hypertrophy, stressful quarantine and a sudden fluctuation in T4 levels due to medication discontinuation can precipitate heart failure in this setting. Other comorbidities may also exist, likely simply due to the age of the cats being treated. In a recent study GI lymphoma was identified in 5% of the cases referred for radioiodine therapy. Considering these concerns I recommend that cats undergo an abdominal ultrasound and echocardiogram/thoracic radiographs to investigate comorbidities before a decision is made to quarantine cats. This helps with their safety during the procedure but also may change the long-term outlook for the patient and thus the decision to treat.

Thyroid storm

The term “thyroid storm” is used to refer to an acute crisis associated with hyperthyroidism that may occasionally be seen in cats. It may be precipitated by stressful situations, such as trips to a veterinary clinic, or by abrupt discontinuation of medication and the associated rise in T4. Clinical signs are generally attributable to the increased sympathetic tone/sensitivity and include tachycardia, panting, hyperthermia, hypertension, agitation and potentially seizures. Treatment involves the use of anti-thyroidal drugs, although these can take days to be effective and so beta blockers (Propranolol 5 mg PO q8 or 0.02 mg/kg IV over 1 minute or Atenolol 1mg/kg IV q12-24) are often used as well to control the signs.

Hyperthyroidism in dogs

Hyperthyroidism in dogs is very rare. It may be seen with iatrogenic over supplementation of levothyroxine for hypothyroidism or other toxic ingestion of the drug. In such instances treatment is simply removal of the drug. More recently cases have been described of dietary hyperthyroidism where dogs have been fed carcasses or carcass components containing thyroid tissue. Again, treatment is simply an alteration in the diet. Naturally occurring hyperthyroidism may occasionally be seen with thyroid carcinomas but these are a rare tumour and only 10% of cases have functional tissue. Thyroid carcinoma is typically characterised by a palpable neck mass in addition to any clinical signs of hyperthyroidism.

Clinical signs of hyperthyroidism in dogs are broadly similar to those described in cats, with PU/PD, polyphagia, weight loss and tachycardia being the most commonly observed signs.

Hypothyroidism in dogs

Introduction

Hypothyroidism is the most common endocrinopathy in dogs and 95% of cases are caused either by lymphocytic thyroiditis or idiopathic atrophy of the thyroid gland, leading to a decrease in thyroid hormone production. Thyroid neoplasia, congenital hypothyroidism and secondary and tertiary hypothyroidism account for the remaining 5% of cases of hypothyroidism.

The diagnosis of canine hypothyroidism is challenging as many clinical signs are nonspecific and can also be identified in dogs with other non-thyroidal diseases. Additionally, the most commonly used assay, total thyroxine (tT4), is non-specific and will be decreased in many dogs that do not have hypothyroidism. Therefore, hypothyroidism should be a clinical diagnosis based on a combination of compatible signalment, clinical signs, physical examination findings and clinicopathological abnormalities, supported by specific endocrine testing.

Diagnosis

Signalment

Hypothyroidism is diagnosed in middle-aged to older dogs with a mean age of diagnosis at 7 years and without apparent sex predisposition. Doberman Pinchers and Golden Retrievers have been reported to be predisposed based on USA data. However, similar findings have not been identified in the UK.

Clinical signs

Thyroid hormones regulate cellular metabolism and therefore clinical signs in hypothyroid dogs are due to the decreased metabolic rate in different body systems.

<table>
<tr><th colspan="4">Clinical Manifestation of Hypothyroidism in the Adult Dog</th></tr>
<tr><th><u>Metabolic</u></th><th><u>Dermatologic</u></th><th><u>Neuromuscular</u></th><th><u>Others</u></th></tr>
<tr><td>Lethargy</td><td>Endocrine alopecia</td><td rowspan="2">Polyneuropathy/myopathy</td><td>Bradycardia</td></tr>
<tr><td>Inactivity</td><td>Seborrhoea</td><td rowspan="2">Female infertility</td></tr>
<tr><td>Weight gain</td><td>Dry hair coat</td><td>Vestibular signs</td></tr>
<tr><td>Cold intolerance</td><td>Pyoderma</td><td rowspan="2">Cranial nerve deficits</td><td rowspan="2">Corneal lipidosis</td></tr>
<tr><td>Mental dullness</td><td>Hyperpigmentation</td></tr>
<tr><td></td><td>Facial myxoedema</td><td></td><td></td></tr>
</table>

Common clinical signs include lethargy, mental dullness, reluctance to exercise, cold intolerance and weight gain without polyphagia. Dermatological signs, especially endocrine alopecia, seborrhoea, scaly skin and superficial pyoderma, are present in 60-80% of hypothyroid dogs. Alopecia is first evident in areas of wear, such as the lateral trunk, ventral thorax, neck and tail (the latter causing the typical “rat tail” appearance) and usually progresses to bilaterally symmetric truncal alopecia. The head and extremities are usually unaffected and pruritus is absent unless there is concurrent pyoderma, which is not uncommon. Coat colour dilution may occur, and failure of hair to regrowth after clipping is common. Other dermatologic changes include hyperkeratosis, hyperpigmentation, comedone formation, hypertrichosis and poor wound healing. Myxoedema (non-pitting oedema) is occasionally seen and is due to the deposition of glycosaminoglycans and hyaluronic acid within the dermis, which bind water. This results in a non-pitting oedema of the skin, particularly in the face and jowls, giving a “tragic” facial expression.

The central and peripheral nervous systems can be affected in hypothyroid dogs. The most common neurological manifestation of hypothyroidism is diffuse peripheral neuropathy causing generalised weakness, ataxia and decreased reflexes. A subclinical myopathy has also been reported in hypothyroid dogs. Cranial nerve dysfunction (facial, trigeminal and vestibulocochlear) with or without abnormal gait has also been reported. Neurological signs may be multifocal, acute or chronic, static or progressive and may occur without other clinical signs of hypothyroidism. The causal relationship between laryngeal paralysis or megaoesophagus and hypothyroidism is still unclear because thyroid supplementation does not consistently improve laryngeal or oesophageal function.

Cardiovascular signs can include sinus bradycardia and a weak apex beat. The ECG of hypothyroid dogs may reveal reduced amplitude R waves and infrequently arrhythmias, such as 1st degree AV block, atrial fibrillation and occasional ventricular premature ectopic beats.

Other clinical signs observed in hypothyroid dogs include reproductive (e.g. female infertility, prolonged parturition, periparturient mortality) and ocular abnormalities (e.g. corneal lipidosis, decreased tear production).

Myxoedema coma is an uncommon but life-threatening presentation of hypothyroid dogs characterised by profound obtundation to coma, hypothermia without shivering, skin myxoedema and severe bradycardia, although not all of these signs occur concurrently in the cases that have been described in dogs.

Haematology and serum biochemistry

Haematology reveals a non-regenerative anaemia in up to 50% of cases. The most common abnormality observed in the serum biochemistry is hyperlipidaemia due to hypercholesterolaemia and hypertriglyceridaemia seen in ≥75% of hypothyroid dogs. Mild increases in ALT and ALKP and CK are not uncommon.

Endocrine testing

This should be reserved for those dogs suspected to be hypothyroid based on compatible clinical signs and clinicopathological findings in order to avoid misdiagnosis. Measurement of tT4 is a very sensitive and therefore useful screening test for hypothyroidism. A tT4 within or above the reference range makes a diagnosis of hypothyroidism very unlikely unless there are anti-T_4 antibodies causing a spurious tT4 increase. However, tT4 is very non-specific as concurrent diseases, and some drugs can decrease tT4 concentration.

Table 2: Various drugs affecting thyroid function tests

Drug	**Total T4**	**Free T4**	**TSH**
Glucocorticoids	↓	↓ or =	=
Phenobarbital	↓	↓	= or ↑
Sulphonamides	↓	↓	↑

It should also be taken into consideration that tT4 concentration is lower in medium and large-breed dogs, declines with age, and sight hounds and sled dogs have lower concentrations than the established laboratory reference ranges. Free T_4 concentration (fT4) measured by equilibrium dialysis is more specific than tT4 for the diagnosis of hypothyroidism and is not affected by the presence of anti-T_4 antibodies. There are other methods available to measure fT4 (e.g. radioimmunoassays, chemiluminescent assays), but there are less accurate and therefore their use is discouraged. However, severe non-thyroidal disease, certain drugs and breed variability can still decrease fT4 concentration. Measurement of basal thyrothropin (TSH) has been suggested as first-line test, along with tT4, for the diagnosis of hypothyroidism. TSH would be expected to be increased in cases of primary hypothyroidism and a combination of low tT4/fT4 and increased TSH is highly specific for hypothyroidism. However, up to 38% of hypothyroid dogs have TSH concentrations within the reference range and TSH concentration may also be increased in dogs with normal thyroid function. This again highlights the importance of thyroid testing exclusively in dogs with a clinical suspicion of hypothyroidism.

In a dog with compatible clinical signs and clinicopathological findings with a low tT4 or fT4 but a TSH within the normal limits, performing a TSH stimulation test can be considered. The TSH stimulation test is considered the gold standard test for assessment of thyroid function in dogs; however, TSH is difficult to source and it is expensive. Alternatively, a therapeutic trial can be considered and it is many times the most practical approach to confirm a diagnosis hypothyroidism. If therapy leads to an improvement of clinical signs within an appropriate time frame treatment should be temporarily discontinued to determine if there is a recurrence of the clinical signs, which would be compatible with hypothyroidism. If there is no response to treatment after 8 to 12 weeks of therapy and a tT4 within the therapeutic range, therapy should be withdrawn and other diagnoses pursued. If repeated thyroid function testing is attempted, it is generally recommended that thyroid hormone supplementation should be discontinued for 6-8 weeks beforehand.

However, the time between the discontinuation of thyroid hormone supplementation and the acquisition of accurate results regarding thyroid gland function depends on the duration of treatment, the dose and frequency of administration of the thyroid hormone supplement, as well as individual variability.

Thyroid imaging

Ultrasonography may be useful in the assessment of dogs with hypothyroidism. The thyroid gland is usually smaller and less echogenic in dogs with hypothyroidism than in dogs with non-thyroidal diseases. However, there is some overlap between groups and finding a low thyroid volume is insensitive for the diagnosis of hypothyroidism. Nuclear scintigraphy allows assessment of thyroid function and has a high discriminatory power in differentiating hypothyroid dogs from dogs with non-thyroidal diseases. However, the availability of scintigraphy is limited to a few specialised hospitals.

Treatment and therapeutic monitoring

The treatment of choice for hypothyroidism is synthetic sodium levothyroxine (l-thyroxine). L-thyroxine has an oral bioavailability of ≤50%, which is further decreased if administered with food hence, it is preferred to be administered on an empty stomach. However, owners could also give levothyroxine with food as long as they are consistent, but the dose needed to reach euthyroidism would be higher. The use of thyroid extracts, thyroglobulin or combinations of l-thyroxine and liothyronine are not recommended because the bioavailability of these compounds is variable, making accurate dosing difficult.

Various licenced L-thyroxine products are available that have starting dose recommendations of once or twice a day. One study indicated that initial twice daily administration at a dosage of 0.02 mg/kg improves the likelihood of response to treatment. If clinical signs resolve and tT4 concentration is within the therapeutic range, then l-thyroxine could be decreased to once daily. Clinical signs and clinicopathologic abnormalities associated with hypothyroidism should resolve within an appropriate time frame with adequate therapy. An increase in mental alertness and activity usually occurs within the first week of treatment and this is an early indicator that the diagnosis of hypothyroidism was correct. Dermatological signs may take several months to completely resolve. Neurologic deficits usually improve rapidly after treatment but complete resolution may take up to 3 months.

Therapeutic monitoring is recommended 6-8 weeks after starting l-thyroxine supplementation, in addition to whenever thyrotoxicosis develops or when there is a poor response to therapy. Therapeutic monitoring is also recommended 2-4 weeks after adjusting l-thyroxine dose or if a different brand of l-thyroxine is used, due to differences in potency and bioavailability.

Serum tT4 concentration should be measured 4-6 hours after l-thyroxine administration in dogs treated twice a day and also before l-thyroxine administration in dogs treated once a day. The measurement of TSH alongside the tT4 increases the cost of therapeutic monitoring. However, it is generally recommended as TSH provides a longer-term assessment of the adequacy of the treatment, unlike tT4, which only provides information regarding the time of blood sampling. For otherwise healthy dogs, the aim is to obtain a tT4 in the upper half or slightly above the therapeutic range 4-6 hours after dosing and if once-daily treatment is being used, pre-pill tT4 should be within the lower end of the therapeutic range. TSH should be low or within the reference range. The dose of l-thyroxine should be adjusted based on tT4 and TSH concentrations but also taking into consideration clinical response, age, presence of concurrent disease and concurrent drug administration. Once clinical signs have resolved and tT4 concentration is within the therapeutic range, long-life monitoring at least every 6 months is recommended as the development of concurrent diseases and differences in gastrointestinal absorption may lead to significant variations in tT4 concentration.

It is not uncommon for hypothyroid dogs to have or develop concurrent diseases given their age. It is not known what the appropriate therapeutic range in hypothyroid dogs with concurrent diseases or receiving drugs such as glucocorticoids or phenobarbital is, but it is likely to be lower than the range for otherwise healthy dogs. Measurement of TSH along tT4 may help to provide treatment recommendations, as a persistently elevated TSH indicates inadequate supplementation or poor compliance.

On the other hand, if TSH is within the reference range, even in the face of a low tT4, and clinical signs attributable to hypothyroidism are absent, there is no need to increase l-thyroxine dose to increase tT4 concentration into the therapeutic range.

Treatment of dogs with concurrent cardiomyopathy or hypoadrenocorticism deserves special mention. Thyroid hormone supplementation increases myocardial oxygen demand, which may lead to cardiac decompensation.

Therefore, the recommended initial dose in these cases should be a 25-50% of the routine starting dose, with progressive dose increments according to the therapeutic monitoring, clinical signs and re-evaluation of cardiac function. Dogs with concurrent hypothyroidism and hypoadrenocorticism should have the latter disease stabilised first because levothyroxine supplementation increases the basal metabolic rate, which may exacerbate electrolytes imbalances in the unstable dog with hypoadrenocorticism.

Early recognition and treatment of hypothyroid dogs with myxoedema coma is critical for survival. Treatment includes l-thyroxine supplementation administered intravenously (5µg/kg every 12 hours) along with intensive supportive care, which involves fluid therapy, slow and passive re-warming and even ventilatory support if respiratory depression is profound. As concurrent disorders commonly precipitate myxoedema coma, diagnosis and treatment of these disorders is critical.

Treatment failure

The most common cause of treatment failure is an incorrect diagnosis as other diseases (e.g. flea allergic dermatitis, hyperadrenocorticism) have similar clinical signs that mimic hypothyroidism and can cause a decrease in thyroid hormones, particularly tT4. In these cases, thorough investigations for the diagnosis of another disease should be undertaken. Less common causes of treatment failure include poor owner compliance or poor gastrointestinal absorption, which can be identified by routine therapeutic monitoring. In cases where there is poor gastrointestinal absorption of l-thyroxine, oral synthetic liothyronine (T3) can be used instead. However, close therapeutic monitoring would be recommended because the risk of iatrogenic hyperthyroidism would be higher.

The prognosis of dogs with primary hypothyroidism receiving appropriate therapy should be excellent with resolution of clinical signs, improved quality of life and a normal life expectancy. The prognosis of dogs with myxoedema coma is dependent on early diagnosis and aggressive treatment.

Hypothyroidism in cats

Congenital hypothyroidism (cretinism) is occasionally encountered in kittens and can occur through several different mechanisms. Kittens are typically normal until around 8 weeks of age but then it is noted that they fail to continue growing and also develop megacolon. If identified and treated early then there can be some improvement but if early treatment opportunities are missed the prognosis is poor.

Hypothyroidism in adult cats used to be considered rare as classic signs, as described for dogs above, are rarely appreciated. More recently it has been recognised that iatrogenic hypothyroidism may occur commonly in cats treated for hyperthyroidism and this may the case in ~20% of cats treated with I^{131}. Hypothyroidism in this setting is defined as the biochemical combination of low tT4 and elevations in cTSH. It appears that this combination is associated with a higher chance of developing azotaemia after treatment and also with the progression of that azotaemia if it is present. Although it has not been demonstrated, many have assumed that if a cat is azotaemic and hypothyroid following radioiodine therapy then it would befit from levothyroxine treatment in order to minimise renal progression. Despite this being the case in a proportion of treated cats, it is generally considered preferable to have an underactive thyroid rather than an overactive one and so radioiodine remains the gold standard therapy.

Hyperparathyroidism

Introduction

There are 4 parathyroid glands, located cranial and caudal to each lobe of the thyroid gland. Primary hyperparathyroidism is typically caused by an adenoma of 1 of these glands, although multiple adenomas are sometimes diagnosed. The parathyroid glands produce parathyroid hormone (PTH) which acts on bones to stimulate calcium release and the kidney to promote calcium resorption and phosphorus excretion, thereby raising plasma calcium concentration and lowering phosphorus. Typically, phosphorus concentrations are not low enough to be associated with neurologic or haemolytic signs and so the principle clinical signs seen is PU/PD. More severe consequences of hypercalcaemia (acute kidney injury, neurologic signs, gastrointestinal signs) are less frequently encountered, perhaps because the low phosphorus concentration prevents aberrant mineralisation.

Diagnosis

Diagnosis of hyperparathyroidism is based on recognition of hypercalcaemia (both total and ionised), exclusion of other causes of other causes of this finding and recognition of an inappropriately normal/elevated PTH (where it should be low). The presence of a low phosphorus concentration together with the hypercalcaemia, in a clinically bright and well patient should alert the clinician to the likelihood of hyperparathyroidism. Other causes are typically easy to rule out most are associated with other clinical signs and more unwell patients. The most common differential diagnoses include mediastinal lymphoma, anal sac adenocarcinoma, hypoadrenocorticism, angiostrongylus, granulomatous inflammation, vitamin D intoxication, renal disease and lytic bone lesions. PTH should be measured to confirm the diagnosis and PTHrp should be measured to rule out unidentified neoplastic causes.

Cervical ultrasound is then typically performed to identify the enlarged parathyroid gland(s) prior to treatment. If multiple enlarged glands are found then secondary hyperparathyroidism (due to renal disease) should be considered. If no enlarged glands are found then the diagnosis should be reconsidered but ultrasound may fail to identify enlarged tissue in situ or if it is ectopic and so the absence of a confirming ultrasound does not exclude the disease.

Treatment

Hyperparathyroidism is typically due to benign disease and has limited long term consequences in many cases. Given that is typically a disease of older dogs, if owners can tolerate the PU/PD and the risk of other consequences, then choosing to ignore the problem may be a valid treatment option. No medical treatment options have been described.

The hypercalcaemia associated with this disease rarely warrants emergency, aggressive treatment as the phosphorus is not high enough to make the calcium x phosphorus product a concern. Nonetheless, a reduction of calcium may be beneficial before prolonged anaesthesia for surgery. This can be achieved through 0.9% saline diuresis at up to 8ml/kg/hr if the patient will tolerate it. Should it be required then additional strategies that can be used include frusemide (1mg/kg IV q6hrs) or glucocorticoids (dexamethasone 0.05mg/kg IV SID) but the latter should only be used once lymphoma has been excluded. Bisphosphonates are occasionally used to control hypercalcaemia in other settings but their use is not typically required for hyperparathyroidism.

Surgery is the traditional treatment of choice to remove the overactive parathyroid tissue. If a nodule is identified, either from ultrasound or at exploration then this should be removed. If no nodule is removed then a hemi-thyroidectomy can be considered to remove 2 glands in the hope that one is causing the problem. On rare occasions ectopic parathyroid tissue has been described and so it may be necessary to explore the neck, from the tongue base to the thoracic inlet, looking for any abnormal tissue.

Ethanol ablation, where the parathyroid nodule is destroyed through ultrasound guided ethanol injection, has been described in a large case series and appears to be a good alternative to surgery in suitably experienced hands. Too little ethanol risks leaving residual tissue behind whereas too much may damage there recurrent laryngeal nerve or the carotid and so caution is advised.

Hypoparathyroidism

Introduction

Hypoparathyroidism is a rare spontaneous disease in dogs but may occur in dogs or cats as an iatrogenic problem of thyroidectomy or parthyroidectomy. In iatrogenic surgical cases it is often transient until residual tissue has hypertrophied but it may be permanent in some instances. The spontaneous disease is always permanent.

The disease is characterised by hypocalcaemia which may manifest as tremors and tetany, which may be continuous or episodic.

Diagnosis

Differential diagnoses for hypoparathyroidism are few as most other diseases associated with hypocalcaemia have a markedly different presentation and labwork. These include acute pancreatitis, sepsis, malabsorption in association with protein losing enteropathy, nutritional hypoparathyroidism, eclampsia, and ethylene glycol toxicity. Although the other diagnoses are highly unlikely, PTH should be measured and confirmed to be low to make the diagnosis.

Treatment

Regardless if treating the spontaneous or iatrogenic forms of hypoparathyroidism, the treatment aim is the same, namely to increase the ionised calcium above 1.0mmol/L to minimise the risk of clinical signs but to keep it below the normal reference range (typically 1.20-1.45mmol/L). As such I advise aiming for around 1.10mmol/L. the reason for keeping the calcium below normal is mainly because this is more likely to stimulate hypertrophy and recovery of normal thyroid tissue. Additionally, treatment is NOT in the form of PTH replacement and so calciuresis will continue. If blood calcium is too high this will only result in more calcium excretion and a greater risk of calcium containing urolith formation.

In animals that are symptomatic for their hypocalcaemia, emergency treatment is warranted. This should be in the form of 1ml/kg 10% calcium gluconate given IV over about 20 minutes, with ECG monitoring. This will only last a few hours and so calcium should be kept up in the short term using a calcium gluconate infusion at 60 to 90 mg/kg/day of calcium (2.5 to 3.75 mg/kg/hr) where the 10% solution contains 9.3mg/ml calcium. Subcutaneous injections (diluted to <5%) can be given as an alternative but there is a risk of calcinosis developing at the injection site so It is not preferred.

In the medium-long term, oral therapy is used to treat hyperparathyroidism and maintain adequate calcium. This should be started as soon as possible as it can take several days to become effective. There is no readily available PTH substitute and so treatment is in the form of Vitamin D which increases intestinal absorption of calcium and phosphorus. Many different Vitamin D preparations are available with the cheaper ones generally being slower/longer acting such as ergocalciferol. Shorter and more rapid acting Vitamin D forms are generally preferred such as calitriol (loading dose of 0.02 to 0.03 µg/kg/day PO for the initial 3 to 4 days and a maintenance dose of 0.005 to 0.015 µg/kg/day PO), AT-10/Dihydrotachysterol (0.03 mg/kg/day PO for 2 days or until effect, then 0.02 mg/kg/day PO for 2 days, and finally 0.01 mg/kg/day PO in divided doses) or alfacacidol (initially 5-15ng/kg/day, but adjusted to effect). For all forms of vitamin D the dose should be divided into at least twice daily dosing.

A normal commercial diet has enough calcium in it to maintain normal blood calcium when combined with additional Vitamin D at full effect but this takes time. Oral calcium supplementation is therefore advised in the first 2-4 months after starting therapy. Calcium carbonate is the preferred salt as it is cheap and non-irritant and the starting dose is typically 25mg/kg elemental calcium q8-12hrs which equates to 62.5mg/kg calcium carbonate.

Following initiation of a calcium gluconate infusion, oral Vitamin D and oral calcium carbonate, the infusion should be weaned off after 2-4 days with careful monitoring of the ionised calcium over that time. Vitamin D should be adjusted to achieve target calcium levels but if the calcium is markedly low then additional calcium carbonate supplementation can also be considered. Once target levels have been obtained then calcium carbonate can be discontinued after a few months, with careful monitoring.

Vitamin D should be continued until calcium levels start to increase and at that point Vitamin D can be cautiously decreased, with monitoring, to see if residual parathyroid tissue has become functional again. Otherwise, dosage of this medication requires periodic checks/adjustments for life to keep it in the desired range.