Emerging feline endocrinopathies - in South Africa

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**Hyperthyroidism:**
The most frequently diagnosed feline endocrinopathy world-wide - now also appearing in SA

**Signalment:** More than 95% of cats with hyperthyroidism are more than 7 years old. Siamese have a decreased risk of being affected.

**Clinical signs:**
1. **Cardiovascular**
   - sinus tachycardia: approximately ½ of hyperthyroid cats at diagnosis. Sinus tachycardia usually resolves with treatment. Other arrhythmias are much less common and also less likely to resolve on return to the euthyroid state - so may reflect co-incident disease
   - systolic murmurs: typically Gr 1-3/6 and typically increase in intensity as the heart rate increases because they’re caused by dynamic LV outflow tract obstruction
   - gallop rhythms: a rapid ventricular filling
   - hyperkinetic femoral pulse
2. **Increased SNS tone**
   - Tachypnoea, panting (may also be a CHF)
   - Tachycardia
3. **Increased metabolic rate**
   - Pp and weight loss. Loss of muscle (mm) mass contributes to the decrease in serum creatinine. Mm catabolism tends to increase BUN
   - Heat intolerance may ppt psychogenic polydipsia and contribute to the pu/pd
4. **Hypertension:** sudden blindness (retinal haemorrhage, oedema, detachment); stroke. Prevalence depends on the study but affects between 9-19% in recent papers. One recent study suggests that some cats become hypertensive after treatment of their hyperthyroidism.
5. **Neuromuscular**
   - hypokalaemia - generalized weakness, neck ventroflexion, ataxia, fatigue, mm tremor
6. **Renal**
   - Renal hypertrophy on palpation
   - RAAS activation which increases glomerular hypertension and causes mild proteinuria as well as hypokalemia. This tends to resolve with treatment even in cats that become azotaemic after treatment.
   - Increased renal perfusion increases Na and water excretion (pressure diuresis) resulting in pu/pd and increases GFR, thus decreasing serum BUN and creatinine. This effect in more pronounced on creatinine (see above).
   - Asymptomatic urinary tract infections are common (12% of non-azotaemic cats).

**Bloods:**
- Erythrocytosis, increased MCV - T4 stimulates erythropoesis and decreases maturation time
- Increased ALT (mild increase in ALP possible)
- Azotaemia 25%
- hyperphosphataemia - altered bone metabolism, hyperPTH (up to 75% of cases in earlier studies)
- hypokalaemia - diuresis
Imaging
- Thoracic radiographs: Left ventricular (LV) and left atrial (LA) enlargement, rarely CHF (2-4% of cases in recent studies)
- Echocardiography: LV hypertrophy (usually subtle), increased fractional shortening (FS), LA and LV dilatation (because of volume loading). FS is the variable that most consistently decreases with treatment. A markedly increased wall thickness or a decreased in left ventricular lumen in diastole should make you consider concurrent HCM.

Diagnosis
1. Total T4: Your most useful test. Total T4 levels do fluctuate during the day, so it is worth repeating in suspicious cases with T4 at the higher end of the normal range, especially if they have concurrent illness.
2. Free T4: This can be run by equilibrium dialysis or an analog assay. Equilibrium dialysis is not run in South Africa. Free T4 by any other method gives no more information than a total T4 - it usually just costs more. In addition, free T4 by equilibrium dialysis is not a good first line screening test because 6-12% of cats with non-thyroidal illness and no evidence of hyperthyroidism will have elevated free T4 while false positives are much rarer when using total T4. Specifically, this test not help separate cats with CRF alone from those with CRF and hyperthyroidism.
3. T3 suppression test: This may help identify hyperthyroidism in sick cats with normal T4 levels.
4. Thyroid scintigraphy: should be available at Onderstepoort by the end of 2011. Facilitates identification of ectopic thyroid tissue.

Treatment: always stabilize with carbimazole first, then decide whether to operate
1. Tachycardia: carbimazole +/- initial beta blockers (propranolol 2.5-5 mg / cat tid). Atenolol (6.25 -12.5 mg / cat sid or 1-2 mg/kg bid) is preferred if the patient has overt congestive heart failure or asthma because it is β1 selective.
2. Control hypertension: amlodipine and / or ACEi depending on severity. Although atenolol will decrease blood pressure, it is insufficient to drop the BP below 160 mm Hg systolic in most cats.
3. Control CHF: frusemide, ACEi, thoracocentesis as indicated.
4. High T4
   - Medical treatment:
     Induction: All cats should initially be stabilized on medical treatment to determine whether renal function will decrease significantly once they become euthyroid. This also allows stabilization of cardiac changes and control of hypertension prior to surgery. Methimazole tastes revolting to cats and has to be formulated specifically for a patient in South Africa. Carbimazole (Neo-mercazole 5 mg) is readily available and most cats take the pills if crushed into their food. Start on 5 mg tid for 1-2 weeks. 90% of cats on tid treatment become euthyroid within 3-15 days (mean 5.7 days) and the length of time needed is correlated with the starting T4 levels. Clinical signs of hyperthyroidism usually take a few days longer to resolve.
     Chronic medical management: Once T4 levels are normal, carbimazole is reduce to bid treatment at the least effective dose. Most cats need 5 mg bid. Many cats on methimazole / carbimazole have T4 levels below the reference range. Although clinical signs of hypothyroidism are rare and surgical risks are not increased, recent studies have shown that median survival of azotaemic cats with low T4 on treatment was half that of azotaemic cats with T4 in the normal range. Thus closer monitoring of T4 levels may be of benefit in a selected group of patients. Total T4 on treatment should be between 10-40 nmol/l. Note that T4 levels return to pre-treatment levels within 2d of stopping carbimazole /methimazole, so client and patient compliance are essential.
Approximately 1/3 of cases become azotaemic after induction of euthyroidism - 17-25% on thyroid medication and 33-49% after radioactive iodine treatment or thyroidectomy. This is more likely to occur in older cats with small/irregular kidneys on palpation. Median survival of cats that became azotaemic while on treatment was no different to those that didn't, thus mild azotaemia that develops after induction of euthyroidism is not a contra-indication to thyroidectomy / radioactive iodine treatment as long as the patient is clinically well.

Undertreating hyperthyroidism is indicated if patient that was previously eating stops eating and is azotaemic - so treat the cat and not the blood test results. It would be unwise to undertreat to maintain the lab results within the reference range because chronic hyperfiltration could, at least in theory, hasten the decline in renal function.

Adverse reactions to methimazole and carbimazole usually develop during the first 3 months’ treatment. 10% of cats on carbimazole may vomit and 5% develop subclinical haematological changes (eosinophilia, lymphocytosis, leukocytosis). Both are transient and usually do not require withdrawal of treatment. Facial pruritus, although much rarer, usually only resolves completely when treatment is stopped. Severe leucopenia (WCC < 0.25 x 10⁹/l) or thrombocytopenia (< 75 x 10⁹/l), positive ANA and Coomb’s tests, and hepatotoxicities (markedly raised liver enzymes) are rare and have only been reported with methimazole. In general, side effects are more commonly reported on methimazole than on carbimazole. Carbimazole is metabolized to methimazole, so it is not clear why side effects appear less frequent.

**Surgery:** Bilateral thyroidectomy with or without parathyroid autotransplantation is most commonly performed as 80% of cats have bilateral disease. Iatrogenic hypoparathyroidism (transient or permanent) is the most common complication. Others include anaesthetic risks in older cats, laryngeal paralysis, Horner’s syndrome, iatrogenic clinical hyperthyroidism, persistent hyperthyroidism if there is functional ectopic thyroid tissue, recurrent hyperthyroidism if the gland was incompletely removed. Parathyroid autotransplantation and staged thyroidectomies may decrease the risk of post op hypercalcaemia. Parathyroid autotransplantation may increase the risk of recurrent hyperthyroidism if thyroid tissue is inadvertently transplanted as well.

After bilateral thyroidectomy, cats should be monitored for hypocalcaemia for 3-7 days. If clinical signs develop (restlessness, abnormal behaviour, muscle cramping, muscle pain, muscle tremors - esp face and ears, tetany, convulsions), treat with i/v calcium gluconate 10% at 1-1.5 ml / kg, calcitriol (Rocatrol) 2.5-10ng/kg/d and oral calcium carbonate (0.5-3g/cat / day in divided doses). Doses that maintain calcium at the low end of the normal range vary between individuals. Some cats may be weaned off treatment weeks to months later (mean of 71 days).

**Radioisotope treatment** with ¹³¹I: will be available soon at Onderstepoort. This is the treatment modality of choice for confirmed thyroid carcinoma and for cats with ectopic thyroid tissue in cats.

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<thead>
<tr>
<th><strong>Prognosis</strong></th>
<th><strong>Median survival times</strong></th>
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<tbody>
<tr>
<td>Decreased survival shown if:</td>
<td>Medical Rx: 417 days, 595 days</td>
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<tr>
<td>Older at the time of diagnosis</td>
<td>Thyroidectomy: approximately 2 years</td>
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<tr>
<td>U Pr:Cr &gt; 0.3 at diagnosis</td>
<td>Radioactive iodine: 2-4 years</td>
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<tr>
<td>Hypertension at diagnosis</td>
<td></td>
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<tr>
<td>Urine SG &lt; 1.024</td>
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<tr>
<td>PCV &lt; 32%</td>
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<td>Azotaemia at diagnosis</td>
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**Hyperaldosteronism (Conn’s disease)**

**Aetiology**
Adrenal hyperplasia
Adrenal tumours: more common; may be bilateral; prognosis similar for carcinoma and adenoma; rarely associated with other endocrineopathies.

Aldosterone physiology:

<table>
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<tr>
<th>Aldosterone release</th>
<th>Effect of aldosterone</th>
<th>Diseases associated with hyperaldosteronism</th>
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<tbody>
<tr>
<td>RAAS activation</td>
<td>Retention of Na and water resulting in expansion of intravascular volume and increased BP</td>
<td>Primary: (independent of renin)</td>
</tr>
<tr>
<td>Increase in extracellular K</td>
<td>Potassium wasting</td>
<td>• adrenal</td>
</tr>
</tbody>
</table>
|                     | progression of renal disease
|                     |                     | • hyperplasia / neoplasia |

Secondary (something activates the RAAS)

• CHF
• Renal disease
• Liver failure

Clinical signs may include
- Hypertension resulting in sudden blindness, renal damage resulting in pu/pd, myocardial hypertrophy and fibrosis causing heart murmurs.
- Hypokalemic myopathy: cervical ventroflexion, hindlimb weakness, paresis
- Palpable abdominal mass

Diagnosis:
- Serum biochemistry: hypokalaemia (not all cases), sodium normal or rarely mildly increased, elevated CK +/- azotaemia CLUE: hypophosphataemia in presence of azotaemia.
- Urine analysis: +/- isosthenuria, proteinuria.
- r/o common DD for these hypertension and hypokalaemia
- Measure serum renin if possible (unstable, special sample handling requirements, CSL run), especially if patient is hypertensive - to r/o secondary hyperaldosteronism (primary disease: low renin; secondary: high renin).
- Adrenal ultrasound: look for an adrenal mass, adrenal calcification and / or abnormal adrenal echogenicity. Bilateral adrenal adenoma are reported. Hyperplastic adrenals may show no or very minor ultrasound changes. NB an adrenal mass as a sole finding does not mean the cat has Conn’s.

Treatment:
- Unilateral adrenal mass without metastasis: Consider surgery - can be tricky with 4/10 cats in the largest case series dying within 14 days because of haemorrhage / sepsis.
- Medical management: spironolactone (1 mg/kg bid), potassium supplementation (2-6 mmol/cat bid kaligel), amlodipine (0.625-1.25 mg/cat/d) +/- ACEi to control hypertension. Note that up to 1/3 cats on spironolactone may develop severe facial pruritus. Treat to resolution of signs not to normalization of K.
- Hypertension is refractory to treatment in some cases.
- Prognosis: 1-2 years on medical treatment, up to 5 years after adrenalectomy. Histopath did not appear to affect prognosis.
Acromegaly

Aetiology: All cats described so far had a tumour, usually an adenoma in the neurohypophysis resulting in excess growth hormone secretion. The normally pulsetile secretion of GH becomes exaggerated in disease. Progesterone induced GH secretion resulting in acromegaly has not been described in cats to date.

Clinical signs: almost all reported cats with acromegaly have or develop insulin resistant diabetes mellitus

- pp may develop independent of DM - caused directly by GH
- initial weight loss from DM is usually followed by weight gain ar organomegaly.
- Worry if your diabetic patient shows weight GAIN despite poorly regulated DM

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<tr>
<th>Catabolic effects of GH</th>
<th>Anabolic effects of IGF-1</th>
<th>Effect of pituitary mass</th>
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<tbody>
<tr>
<td>Insulin antagonism and hyperglycaemia - pu/pd and pp. Often need &gt; 2 IU/kg insulin bid Lipolysis</td>
<td>Organomegaly (extremities and viscera) - HCM: murmur, gallop, CHF late - Renomegaly: CRF - Hepatomegaly - Respiratory stridor - Increased size - Increased interdental space - Large tongue - Prognathia inferior - DJD in multiple joints</td>
<td>Lethargy Adipsia Anorexia Loss of regulation of body temperature Circling Seizures Rarely: concurrent endocrinopathies</td>
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Diagnosis: cannot be made based on 1 test

- Serum biochemistry: Typically consistent with DM. Excess GH may cause hyperphosphataemia, mild erythrocytosis and persistent hyperproteinaemia (as high as 95g/l) in some individuals
- Serum IGF-1: good screening test but both false +ve and false -ve possible.
- GH: Few labs run this (http://www.uu.nl/faculty/veterinarymedicine/en/labs_services - Utrecht vet school). Not specific: 61% of cats with HCM had GH levels that overlapped broadly with acromegalic cats.
- Contrast CT / MRI: only practical option in SA. False -ve possibly early in the course of the disease. Does not confirm GH hypersecretion, only that there is a mass. DD pituitary dependent Cushings, but clinical signs should allow differentiation (weight loss, fragile skin (easily torn), patchy asymmetrical alopecia, easy bruising, marked pot belly, folded edges of ears (rare))
- Histopath

Treatment options:

1. Radiotherapy: most accessible option. The response varies from resolution of all signs, others just have improved diabetic control to none at all. Acromegaly may recur after 6-18 months.
2. Hypophysectomy: gold standard treatment in man. Canine hypophysectomy only really done routinely at Utrecht vet school and they’ve only done a few cats.
3. Medical treatment: high doses of insulin to control DM. Because GH secretion is pulsetile, some cats on ultrahigh doses do have sudden life threatening hypoglycaemic episodes. This can be partially avoided by checking blood glucose prior to every insulin injection. The other option to avoid hypos is to limit insulin doses to a maximum of 15 IU / cat / dose\textsuperscript{5,15}.

4. People have tried dopamine antagonists (selegeline)\textsuperscript{1} and somatostatins

\textsuperscript{\S} Short acting somatostatin analogue (Octreotide) may work in a small proportion of cases (1/5 cats)\textsuperscript{1}. An i/v test dose could be used to identify suitable candidates.\textsuperscript{15,21}

Prognosis:

- Medical treatment: survival 4-42 months (median 21 months)\textsuperscript{17}. Most cats with acromegaly die because they develop CHF, progressive CRF or debilitating neurological signs \textsuperscript{5,17}.
- Linear accelerator (11 cases): 1-60 months (median 25 months)\textsuperscript{20}

References: