Updates in Diagnosis and Management of Thyroid Disease

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Goals for this Presentation

Feline Hyperthyroidism

- Etiology
- Diagnosis
- Treatment
- AAVP Feline hyperthyroidism guidelines
- Hyperthyroidism and concurrent disease
- Canine Hyperthyroidism Canine Hypothyroidism

Feline Hyperthyroidism

Common endocrinopathy

- ~10% of cats >10 years of age in US
- Excess circulating active T3 and T4

Adenomatous hyperplasia (>95%)

- Bilateral (70%)
- Rarely thyroid carcinoma (<2%)

Etiology:

- No single risk factor identified
- Multifactorial

Etiology

Genetics

Siamese and Burmese decreased incidence

Husbandry

- Indoor
- Longer life span
- Commercial cat food

Exposure

- Bisphenol-A
- Soy isoflavones
- Polybrominated diphenyl ethers (PBDE) flame retardants

Flame Retardants & Hyperthyroidism Is there a connection?

- PBDE's phased out in 2004 and replaced with organophosphate esters (OPEs)
- Recent article associating TDICPP (an OPE) exposure to hyperthyroidism
 - Silicone tags, ≥7 yr, 78 cats
 - TDCIPP concentrations were higher in hyperthyroid tags vs nonhyperthyroid tags

Guilt by Association

Higher TDCIPP:

- Air freshener use
- Residences built after 2005
- More exposure to upholstered furniture



Establishing The Diagnosis

Clinical signs

- PU/PD, polyphagia, weight loss
- Vomiting, diarrhea
- Vocalization, agitation
- Apathetic hyperthyroidism
- Physical exam findings
 - Palpation of a thyroid nodule
 - Poor hair coat
 - Tachypnea, tachycardia
- Thyroid function testing....

2016 AAFP Feline Hyperthyroidism Guidelines

Importance of a good history and physical exam

- Early diagnosis
- Role of comorbidities

Diagnosis:

- Clinical signs and exam findings AND
- Thyroid function testing
 - Persistently elevated T4
 - Elevated T4 and fT4ed

Thyroid testing

Snap test vs. reference laboratory

- Full CBC, chemistry, UA
- Avoid quality control issues

fT4 vs TT4

- Never assess alone!
- Elevated fT₄ without elevated TT₄, thyroid nodule, or clinical signs is unlikely clinically significant.
- Specificity of total T4 nearly 100%

Summary of the categorical approach to diagnosing suspected feline hyperthyroidism

After evaluating signalment, history, physical exam and a minimum database, patients will present as:



FHT = feline hyperthyroidism; NTD = non-thyroidal disease; T4 = total serum thyroxine concentration; fT4ed = free thyroxine measured by equilibrium dialysis; T3 = triiodothyronine; PE = physical exam



1. Classic Hyperthyroid

- Clinical signs
- Elevated T4

→ Start Treatment....



2. Possible Hyperthyroid

Clinical signs present but T4 normal

→Evaluate for other disease as a cause of clinical signs

- Diabetes mellitus
- Gastrointestinal malabsorption, maldigestion
- GI neoplasia
- CKD

Repeat thyroid testing consider fT4, TSH, thyroid scintigraphy



3. Incidental Palpable Thyroid Nodule

- No clinical signs
- Enlarged thyroid
- Normal thyroid testing
 - If high normal ref. range consider repeat TT4 and fT4

→Repeat T4 in 6 months



4. Subclinical Hyperthyroid

- No clinical signs
- Increased T4
 - Likely early disease
- →Repeat testing in 2-4 weeks
 - Consider TT4 and fT4



5. Hyperthyroid and Additional Disease

- Clinical hyperthyroidism
- Increased T4
- And concurrent disease

→Treat hyperthyroidism and concurrent disease



6. Incidental T4 Elevation

- No clinical signs
- No nodule
- Increased T4

→Repeat T4 Is T4 persistently elevated?

Similar to Group 4

Measurement of Canine cTSH

- Canine-specific TSH validated for cats
- Reference range in senior cats
 - < 0.03 to 0.15 ng/ml
 - Sensitivity but not specific for hyperthyroid cats
 - Increased TSH with low TT4 highly specific for hypothyroidism
- TSH should be < 0.03 ng/ml in cats with clinical hyperthyroidism
- Suppressed in 98% of hyperthyroid cats

Wakeling 2008; Wakeling 2011, Peterson JVIM 2015 & JSAP 2017

Hyperthyroidism The Challenging Diagnosis

- Clinical signs are subtle or absent
- Physical exam findings are subtle or absent
- Questionable thyroid nodule
- Serum TT4 may be in the reference range
- Concurrent disease

Comorbidities

- Thyrotoxic heart disease
- Hypertension
- Retinopathy
- CKD \rightarrow To be continued...
- Gastrointestinal disease
- Insulin resistance

Hyperthyroidism is life threatening

Thyroid storm

Rare, life threatening complication Rapid increase in thyroid hormone

- Palpation
- Withdrawl of treatment
- Anesthesia/stressful event
- Non thyroidal illness

Treatment-

- Atenolol 6.25mg PO q 24
 - If event can be anticipated, give 24 hour prior to event
- Anti-thyroid medication

Treatment Options

- Medical- methimazole
- Dietary- Hills y/d diet
- Surgical
- Radioactive iodine

What can owner afford? How old is cat? Comorbidities or Concurrent Disease?

Antithyroid Drugs

Methimazole – 1.25-2.5 mg PO q 12

- Titrate to effect
- Oral or transdermal
- Can give q 24, but only ~50% controlled

✓ Reversible, but requires daily admin

- ✓ High response rate
- ✓ Frequent lab monitoring
- ✓ Drug reactions

What Monitoring is Required?

CBC, chemistry panel, TT4 TSH? Urinalysis? Frequency:

- Every 2-3 weeks for 3 months
- Then every 3-6 months

Costly.. Owner compliance?

Methimazole-Induced Adverse Effects

Occur in < 5% of cats and usually within 8 weeks of initiating treatment

- Vomiting, inappetance, lethargy

 transient
- Facial excoriations
 stop drug
- Decreased WBCs, RBCs, Plts stop drug
- Hepatotoxicity
 stop drug

stop drug

Myasthenia gravis

Dietary Therapy

Hills y/d is a iodine deficient diet

- Dietary iodine needed for thyroid hormone synthesis
- Simple, high response rate
- Similar to g/d diet- Phosphorous controlled, supplemented with Omega-3s, high quality protein
- 75% of cats had a reduction in T4 at one month

Challenges to Dietary Management...

- Compliance-
 - Multi-cat household
 - Indoor/Outdoor lifestyle
- Compounded medication/supplements
- Concurrent disease altering needs
- Can take months for T4 to normalize

What Have We Learned About Dietary Management?

- TT4 normalized in..
 - 42% of cats in the first 2 months
 - 83% of cats in 2-6 months
- Body weight did not significantly increase, and heart rate did not significantly decrease
- Unknown long term effects of iodine restriction

T. Hui et al. JVIM 2015 Jul-Aug: 29(4):1063-1068

Radioactive iodine

- Kills abnormal cells
- 95% cure rate, permanent
- Often considered treatment of choice
- Limited testing needed after treatment
- Requires specialized facility
- Limited exposure post treatment to minimize human exposure

Treatment Indications for I 131 Treatment

- Routine treatment of hyperthyroidism
- Bilateral disease
- Ectopic thyroid location
- Thyroid carcinoma
 - Identify metastatic lesions
- Adverse effects to medical management

Surgery

- 35-60% cure with unilateral surgery
- Not reversible
- Risk to parathyroid damage
- Requires anesthesia
- Rarely performed
- Requires medical therapy first to control thyrotoxicosis

Goals Regardless of Therapy

- Improved physical condition
- Monitor BCS and body weight
- Goal T4 1-2.5 µg/dL, except when known renal insufficiency
- Monitor renal parameters
- Adverse effects from treatment
- Evaluate for non-thyroid disease
- Monitor for hypothyroidism

latrogenic Hypothyroidism (IH)

- Iatrogenic hypothyroidism can impair renal function
- IH prevalence- 20% of cats
- cTSH validated for use in cats
- Elevation in cTSH may indicate that azotemia secondary to IH
- Cats that developed azotemia following treatment were 2X's more likely to have elevated cTSH

Aldridge, et al. JVIM 2015

latrogenic Hypothyroidism

- High serum cTSH best identifies feline iatrogenic hypothyroidism and differentiates it from non-thyroidal illness syndrome in cats that develop azotemia after treatment
- If hypothyroid consider supplementation with L-thyroxine at 0.01-0.02mg/kg Q 24hr

Lets think about a case...





'Sebastian' 14 yr MC DLH

Presented for vomiting, TT4 5.5 ug/dl

- 3 months later presented for poorly controlled hyperthyroidism (FHT) and I 131 treatment
 - Persistent vomiting, diarrhea, weight loss with a poor appetite
 - TT4 7.5 ug/dl

Medications:

Methimazole 7.5mg PO BID
'Sebastian' 14 yr MC DLH

- Abdominal ultrasound showed diffuse muscularis thickening and mass lesion in duodenum
- FNA confirmed large granular cell lymphoma

Concurrent disease, poor drug absorption

'Sebastian' 14 yr MC DLH



Case Approach:

- Is diagnosis correct?
- Is treatment appropriate?
 - Drug
 - Dose
 - Route
- Could this animal have intestinal disease or other disease process altering drug absorption?
- Or causing clinical signs?

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11/17/01



RDVM: Dr. Cathy Glahn Presented for weight loss

DOB:

- TT4 3.5 $\frac{3047}{400}$ For a ve The in Sa 92780, Tel: 949-559-7289 Fax: 949-559-6727 $\frac{1000}{400}$ For a Blvd (1000) For a • 900-477-4453 • Fax: 949-559-6727
- •fT4 3.7 ng/dl (RR 0.59-3.04)

Started on methimazole 0.625 mg PO BID

• TT4 1.3; BUN 32, Cr 1.3, USG 1.020

'Marble' 14yo FS DSH

- Owner elected to pursue I 131
- Treated without complication
- Presented 1 month later for evaluation of progression of kidney values
 - BUN 36, Cr 2.3
 - Should we have treated?

"We are just fooling ourselves into thinking we are doing something good for the kidneys by leaving the cat hyperthyroid and reducing the degree of azotemia when in the long run it's damaging."

Treating hyperthyroidism unmasks the azotemia, it does not create it.

CKD and Hyperthyroidism

- 10% of cats are azotemic at diagnosis
- 15-49% of cats are non-azotemic at the time of diagnosis and become azotemic after treatment
- Numerous studies have failed to identify parameters that predict azotemia
 - Including USG, proteinuria, and creatinine concentration prior to treatment

Cannot predict prior to treatment!

What about SDMA?

High serum SDMA concentration in a hyperthyroid cat may help predict development of azotemia after treatment

High diagnostic test specificity (97%) but relatively low sensitivity (33%)

So what does this mean?

- If SDMA increased → may become azotemic after treatment
- If SDMA normal→ can still become azotemic following treatment

Peterson et al. JVIM 2018, Jan; 32(1): 295-304

CKD and Hyperthyroidism

- No difference in survival in cats post treatment that developed azotemia vs non-azotemic, unless became hypothyroid
- Important to follow post treatment
 - 1, 3, and 6 month follow up
 - If hypothyroid consider supplementation with L-thyroxine
 - 0.01-0.02mg/kg Q 24hr

FHT and CKD Identified at Initial Diagnosis

Treatment recommendations vary with degree of CKD

Iris staging

- Stage I-IV
- Hypertension
- Proteinuria

Iris Staging	R	P	P		
for CKD	Stage 1 No azotemia	Stage 2 Mild	Stage 3 Moderate	Stage 4 severe	
Creatinine in mg/dL Stage Canin	e <1.4	1.4–2.0	2.1–5.0	>5.0	
stable creatinine Felir	e <1.6	1.6–2.8	2.9–5.0	>5.0	
SDMA in µg/dL	>14	>14	Moderately increased	Markedly increased	
		≥25			
Consider understaged based on creatinine			≥ 45		
UPC ratio Substage Canir	e Nonproteinu	Nonproteinuric <0.2 Borderline proteinuric 0.2–0.5 Proteinuric >0.5			
proteinuria Felir	Nonproteinuric <0.2 Borderline proteinuric 0.2-0.4 Proteinuric >0.4				
Systolic blood pressure in mm Hg Substage based on blood pressure	Normotensive <150 Borderline hypertensive 150–159 Hypertensive 160–179 Severely hypertensive ≥180				

Non Azotemic Cat

- FHT increases GFR and decreases body mass which decreases circulating creatinine
- About 20% to 25% of hyperthyroid cats without known CKD develop azotemia after successful treatment
 - Irrespective of therapeutic modality
- Cannot predict response
- Methimazole trial provides a preview
- Discuss pros and cons with owners

Iris Stage I or Stage II CKD

- Treat with reversible therapy first to preview response
- Initial low dose and dose escalate
 - Methimazole 1.25mg PO q 24
- Monitor carefully
- Stable renal values noted, may consider a more permanent treatment option

Stage III or Stage IV CKD

- Reversible anti-thyroid therapy only
- May need to decrease the dose or stop it all together based on response
- Mild hyperthyroid state may give the best short-term clinical result
- Guarded to poor prognosis
- Uncontrolled hyperthyroidism is damaging to the kidney

Balancing Act



Key Points FHT and CKD:

- Balancing act
- Reversible treatment options
- Cachexia increases BUN, decreases Cr
- Evaluate blood pressure, proteinuria
- Monitor body weight and BCS
- Stage prior to treatment
- Re-evaluate!
- Important to monitor BCS/PE findings

Apathetic Hyperthyroidism

Small Percentage of cats (5%)

Clinical signs:

- Depression
- Apathy
- Weakness
- Weight loss with a poor appetite

Important to evaluate for concurrent illness

Hyperthyroid and Heart Disease

Hypertension?

- Which do I treat first? Is patient visual?
 - Treat both if non-visual or systolic >200
 - Control FHT then consider weaning off amlodipine
 - If systolic <180, treat FHT and reassess

Evidence of CHF?

- Treat both FHT and CHF, regular monitoring once pet becomes euthyroid
- Echocardiogram vs. NT-proBNP

Hyperthyroid and Diabetes

- Insulin antagonism
- Diet?
- Challenges to monitoring:
- Clinical signs overlap
- Hyperthyroidism can have a profound effect on protein metabolism and therefore on serum fructosamine concentrations

→decreases fructosamine independent of BG concentration

Canine Thyroid Disease



Canine Hyperthyroidism

Etiology

- Neoplasia
- Diet
 - Sporadic cases of exogenous thyrotoxicosis

Diagnosis-

- Usually straight forward
 - Total T4
 - Thyroid ultrasound
 - Advanced imaging
 - Scintigraphy

Canine Thyroid Tumors

- Only 10% are functional
- Rarely ectopic
 - Base of the tongue to the base of the heart
- 2/3 are localized to one lobe
- Most common carcinoma

Canine vs Feline

	Canine	Feline
Thyroid tumor	Common	Rare
% Malignant	80-90%	5%
Local Invasion	Common	Rare
Metastatic Behavior	Common	Rare
% Hyperthyroid	~10%	>95%

Treatment for Canine Thyroid Tumors

- Methimazole
- Surgery
- Radioactive lodine
- Radiation
- Chemotherapy

Canine Hypothyroidism

Clinical presentation

- Lethargy
- Weight gain
- Hair coat/skin changes
- Often non-specific

Basic lab evaluation findings:

- 75% are hypercholesterolemic
- 25% have a non-regenerative anemia
- Mild elevation in liver enzymes

Diagnosis

- Low resting T4 alone should not be considered diagnostic
 low specificity
- TSH concentration not sensitive
 - ~25% hypothyroid dogs have normal cTSH
 - ~10% of normal dogs have elevated cTSH

Drugs that Lower T4 Concentrations

- Phenobarbital
- Trimethoprim-sulfonamide
- Glucocorticoids
- Zonisamide
- Clomipramine
- Aspirin
- Carprofen

Breed Variation

Sighthounds

- Greyhound!
- Whippet, saluki, Irish wolfhounds
 Nordic Breeds

Decreased total T4 and fT4

Canine Hypothyroidism Interpretation of Canine TSH

- Don't use TSH as only test for hypothyroidism
- Increased TSH supports hypothyroidism
- Normal TSH does not rule out hypothyroidism
- Return of TSH into normal range supports adequate treatment of hypothyroidism

Canine Hypothyroidism Establishing the Diagnosis

Appropriate history and physical findings Hyperlipidemia ± mild anemia Serum total $T_4 < 0.5 \text{ ug/dl}$ (6 nmol/L) Serum free $T_4 < 0.5 \text{ ng/dl}$ (6 pmol/L) Serum cTSH > 0.6 ng/ml **Positive thyroglobulin autoantibody** (TGAA)

Canine Hypothyroidism Ideal diagnostic panel

T4, fT4ed, TSH

- TSH response test- unrealistic in clinical practice
- Consider Breed \rightarrow unlikely DX
 - Sight hounds
 - Basenjis
 - Athletic animals

Can a dog look clinically hypothyroid and have normal or high TT4?

• T4 can be elevated due to autoantibodies cross-reacting

fT4 should be low



Hypothyroidism in the Literature

- Canine hypothyroidism associated with...
- Gall bladder mucocele Recurrent pyoderma
- Megaesophagus ? Lipemic uveitis
- How long after levothyroxine withdrawl do you have to wait to assess thyroid function?
- A 2017 study supports 1 week, if treated for 16 weeks or less

Central hypothyroidism may be under diagnosed in Miniature Schnauzers

TT4 is low, should I start treatment?

- Are there clinical signs?
- Is there biochemical evidence?
- Is TSH elevated?
- Could medications be altering TT4?
- Could the animal be sick euthyroid?
- Will it hurt my patient to treat them?

Trail for 2-3 months, if no improvement reconsider diagnosis

Treatment

Levothyroxine 0.02mg/kg/day PO either q 24 or divided q12

Many start higher; 0.02mg/kg PO q12 initially

A Pivotal Field Study to Support the Registration of Levothyroxine Sodium Tablets for Canine Hypothyroidism

Victoria A. Lewis, DVM, RPh*, Carla M.K. Morrow, DVM, PhD, DABVT, Johnny A. Jacobsen, DVM, MSc, W. Eugene L PhD, DABVT[†]

From LLOYD, Inc., Shenandoah, Iowa (C.M.K.M., W.E.L.); and AlcheraBio LLC, Edison, New Jersey (V.A.L., J.A.J.).

Lewis et al. JAAHA 2018

Canine Hypothyroidism Therapeutic Monitoring

Goals of therapy:

Resolution of clinical signs 4 to 6 hour post-pill T₄: 1.5 to 5.0 ug/dl TSH less than 0.5 ng/ml

If T4 below target range, increase by 25% and retesting in 2-4 weeks

Once dose established, recheck q 6 months.

Treatment failure?

Key Points:

- Diagnosis (hyper or hypothyroid) is never based on T4 alone
- Hyperthyroid cats can have different presentations
- Treatment recommendations for hyperthyroidism should be case based
- Important to consider possible concurrent diseases in both diagnosis and treatment of hyper or hypothyroidism




Questions?

