Hyperadrenocorticism

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Basic endocrinology

- Hypothalamus
- Pituitary gland
- Functional organ
  - Thyroid gland
  - Adrenal gland
  - Sex organs

Endocrine disorders

- Deficient hormone production
  - Primary - destruction of gland (e.g. Hashimoto’s thyroiditis)
  - Secondary - lack of stimulation to gland (e.g. lack of TSH)
  - Tertiary – lack of hypothalamic stimulation

Endocrine disorders

- Excessive hormone production
  - Primary - glands secrete excess (e.g. adrenal tumor)
  - Secondary - overstimulation of gland (e.g. excess ACTH production)
  - Ectopic production - abnormal cells secrete hormone (e.g. ACTH secretion by small cell carcinoma of lung)

Endocrine disorders

- Defective hormone synthesis
  - genetic defect
  - does not always lead to deficiency
- Resistance to hormone action
Endocrine disease

- Hormones affect multiple organs
  - Broad range of clinical signs
- Diagnosis is not always easy
- Most have multiple tests that are available

Endocrine disease

- Test assessment
  - Sensitivity
    - Percentage of patients with the disease that test positive
    - Trust NEGATIVES
  - Specificity
    - Percentage of patients without the disease that test negative
    - Trust POSITIVES

Hyperadrenocorticism

- Hypothalamus
  - Corticotropin releasing hormone (CRH)
- Anterior lobe
  - Releases ACTH
    - Stimulates adrenal glands
      - Pars distalis
        - CRH
      - Pars intermedia
        - Dopamine

Adrenal glands

- Located cranial to each kidney
- 2 functional zones
  - Medulla
    - Catecholamines
      - Epinephrine
      - Norepinephrine
    - Pheochromocytoma

Adrenal Glands

- Adrenal cortex
  - Zona glomerulosa
    - “Salt”
    - Aldosterone
  - Zona fasciculata
    - “Sugar”
    - Cortisol
  - Zona reticularis
    - “Sex”
    - Androgens
Hyperadrenocorticism

- Cushing's Disease
  - Pituitary dependent
  - Adrenocortical dependent
  - Iatrogenic

- Pituitary disease
  - 85% of cases
    - Anterior pituitary
      - 70%
    - Intermediate lobe
      - 30%
    - Microadenoma
      - 75-90%
    - Macroadenoma
      - 10-25%

- Adrenal disease
  - 95% neoplasia
    - 50% benign
    - 50% malignant
      - >2 cm diameter
        - Carcinoma
      - 5% hyperplasia

Iatrogenic

- Due to exogenous steroid administration
- ANY form
- Clinical signs identical
- Don’t get confused
  - Addisonian if withdrawn suddenly!!

Signalment

- Canine PDH
  - Poodle, Dachshund, Beagle, Boxer, Boston Terrier
    - 75%
      - <20 kg
      - median age: 7-9 yr
      - female = male
- Canine AT
  - Large breeds
    - 50%
    - median age: 10-11 yr
    - female: male = 3:1

Clinical presentation

- Polyuria / Polydipsia
  - 90%
  - Secondary NDI
- Polyphagia
- Muscle atrophy/weakness
- Pendulous abdomen
  - Hepatomegaly
- Recurrent infections
  - Urinary tract
  - Skin
Clinical presentation

- Skin disease
  - Alopecia
  - Rat tail
  - comedones
  - thin skin/bruising
  - hyperpigmentation
  - calcinosis cutis
- Panting
  - Decreased pulmonary compliance
  - Pulmonary hypertension
  - Direct effect on resp. center

Clinical presentation

- Diabetes mellitus
  - Insulin resistant
  - >2.2 units/kg/injection

Clinical presentation

- Hypercoagulability
- Hypertension
- Sudden retinal degeneration
  - SARDS

Clinical presentation

- Macroadenoma
  - Neurologic signs
    - Seizures
    - Ataxia
    - Lethargy
    - ANOREXIA

Cats

- Clinical signs similar to dogs
  - PU/PD
  - Polyphagic
  - Pot bellied appearance

Cats

- Skin fragility
  - Decreased collagen strength
  - Skin will tear when handling
Clinical Pathology

- Routine bloodwork
  - Stress leukogram
  - Increased platelet count
- Urinalysis
  - Isosthenuria
  - Proteinuria
  - UTI
  - +/- glucosuria

Clinical Pathology

- Serum Chemistries
  - Increased alkaline phosphatase
    - Most consistent finding in Dogs
    - Not specific
    - 10:1 ratio of ALP : ALT
    - Not common in cats (15%)

Clinical Pathology

- Diabetes
  - 10% of dogs
  - 95% of cats

Clinical Pathology

- Hypertension
- Radiography
  - Hepatomegaly
  - Bronchial calcification
  - Adrenal calcification
    - Dogs
- CT/MRI
  - Brain
    - Micro / Macroadenoma
  - Abdomen
    - PDH vs. Adrenal dependent
- Ultrasound

Ultrasound

- Adrenal glands
  - Visible 80% of normal animals
    - Dogs <0.8 cm diameter
    - Cats <0.5 cm diameter
  - Significant overlap between normal and abnormal
    - 50% of PDH have “normal” adrenal sizes

Adrenal testing

- ABSOLUTELY REQUIRED
- Screening vs. differentiation tests
- No test is perfect
### Screening tests

- Used to **DIAGNOSE** Cushings
- Urine cortisol : creatinine
- ACTH stimulation test
- Low dose dexamethasone suppression test (LDDST)

### UCCR

- Urine sample collected by owner at HOME
  - Any stress will likely make positive
    - Vet’s office
  - First morning sample
  - Ideally multiple days
    ± combine samples

#### UCCR

- Excellent screening test
  - Sensitivity
    - 100%
  - Specificity
    - 20%
- If positive
  - Perform further tests
    - Help to convince owner to spend money
- If negative
  - Very unlikely to have Cushings

### ACTH stimulation test

- Measures adrenal response to maximal ACTH stimulation
  - ACTH gel
    - 2.2 IU given IM
    - Pre
      - 1-2 hr post
  - Synthetic ACTH
    - 5 ug/kg IV
    - Pre
      - 1 hr post
    - Same protocol for cats

#### ACTH stimulation test

- Normal
  - 5-18 ug/dL post
- Natural Cushings
  - Exaggerated response
    - >22 ug/dL
  - Borderline
    - 15-20 ug/dL
- Sensitivity
  - PDH 65%
  - AT 60%
- Specificity
  - 85-90%
  - Cats?????
ACTH stimulation test

- Controversial
  - vs LDDST

- Gold standard
  - Concurrent disease
    - Kidney dz
    - Diabetes
    - etc
  - Iatrogenic Cushing’s
  - Hypoadrenocorticism
  - Monitoring therapy

LDDST

- Low dose dexamethasone suppression test
- Takes advantage of normal feedback of cortisol
- 0.01 mg/kg dexamethasone IV or IM
  - Cats 0.1 mg/kg

Low dose dexamethasone suppression test (LDDST)

- Blood samples
  - Baseline
  - 4 hour
  - 8 hour
- 8 hour sample used for screening
  - >1.4
    - Positive for Cushing’s
- 4 hour sample may be used for differentiation
  - 65% of dogs

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<th>4 hr</th>
<th>8 hr</th>
<th>Result</th>
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<td>&gt;1.4</td>
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If cortisol suppresses <50% of baseline
- PDH
If not...
- 50:50
- PDH vs AT

Baseline | 4 hr | 8 hr | Result |
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### LDDST

- **Sensitivity**
  - 95%
- **Specificity**
  - As low as 44%
  - Concurrent disease
  - Unknown in cats
- **Cost**
  - Dexamethasone is cheap
  - 8 hour test vs 1 hr

### ACTH stim vs LDDST

**ACTH stimulation**
- 1 hour
- Sensitivity 60-85%
- Specificity 85-90%
- No differentiation

**LDDST**
- 8 hours
- Sensitivity 95%
- Specificity 44%
- 65% differentiate PDH vs AT

- Concurrent disease
- Exposure to steroids
- Monitoring therapy

- No concurrent disease
- No exposure to steroids
- Trust negative test in cats
  - Positive?
### Differentiation tests

- **Used ONLY after have diagnosis**
- **Differentiate between PDH / AT**
  - High-dose dexamethasone suppression test
  - Endogenous ACTH
  - Ultrasound
  - CT/MRI

### Differentiation tests

- **High Dose Dexamethasone Suppression Test**
  - 0.1 mg/kg Dex IV
    - 1.0 mg/kg cats
  - Pre and 8 hour post
    - <50% of baseline PDH
    - <1.4 ug/dL PDH
    - >50% of pre value PDH or AT

### Differentiation tests

- **eACTH**
  - Measures natural ACTH in blood
  - PDH
    - Elevated
    - Adrenal tumor
    - Decreased
  - Expensive
    - ACTH degrades quickly
      - Aprotinin / trasylol
      - Freeze sample

### Differentiation tests

- **Ultrasound**
  - 80% success rate
    - Easier with PDH
      - Both adrenals visualized
    - AT
      - Opposite adrenal atrophied
  - CT / MRI
    - Excellent for AT
      - Determine if vascular invasion exists
      - Metastasis

### Treatment

- **Varies with type of disease**
  - PDH vs AT
  - Macro vs microadenoma
  - Dog vs. Cat

### Treatment

- **Expensive to treat**
  - Multiple visits
  - Repeated ACTH stims
  - +/- Medication
  - Life long therapy
  - Disease **NOT** typically life threatening in dogs
    - It’s annoying to owners
Medical therapy

• Treatment of choice for PDH in dogs
  – Microadenoma

• Medications available
  – Lysodren
  – Trilostane
  – Ketoconazole
  – Selegiline (Anipryl)
  – Metyrapone

Mitotane (Lysodren®)

• Classic drug for dogs
• Cytotoxic to adrenal glands
  – Destroys zonae fasciculata and reticularis
• Some still consider “gold standard”
  – Destroys adrenals
    • True therapy
    • Most research
• Induction vs maintenance phases

Mitotane (Lysodren®)

• Induction
  – PDH dose
    • 50mg/kg/day
    • If diabetic: 25 mg/kg daily
• Endpoints
  – Decreased thirst
    • <100 ml/kg/day
  – Decreased urination
  – Decreased appetite
  – Decreased activity

Mitotane (Lysodren®)

• 5-7 days later
  – ACTH stimulation
    • 1-5 ug/dl
• Average induction: 12 d
• 85% success rate in control

Mitotane (Lysodren®)

• Maintenance phase
  – 50mg/kg/week
  – Recheck
    • 3 weeks
    • 3 months
    • Every 6 months
  – Approx 50% of dogs will relapse during 1st year
Adverse effects

- Relatively common
  - 25% during induction
  - 33% during maintenance
- Lethargy
- Weakness
- GI
  - Vomiting
  - Diarrhea
  - Anorexia
- Neurologic
  - Ataxia
  - Seizures
  - Macroadenoma

Adverse effects

- Adrenocortical destruction
  - Addison’s disease
- Usually reversible
  - May take several months
  - Prednisone therapy
- Irreversible
  - 6% of dogs

Adverse effects

- If owner has ANY concerns
  - Stop Lysodren
  - Administer prednisone
  - ACTH stim
  - Electrolytes
- Question: is it
  - Direct toxicity
  - Macroadenoma
  - Glucocorticoid insufficiency
  - Mineralocorticoid insufficiency

Lysodren® (Mitotane, o,p’-ddd)

- AT
  - Much less responsive to therapy than PDH
- Goal
  - Cortisol undetectable
- Dose
  - 75-100 mg/kg/day
  - >100 mg/kg/week maintenance
  - May have toxicity before control

Trilostane

- FDA approved in US in 2009
- Competitive inhibitor of cortisol production by the adrenals
  - 3β-hydroxysteroid dehydrogenase
  - Does not destroy the gland itself
    - Blocks pathway
    - Reversible?

Trilostane

- Not as much research on this drug
- 2009
  - Starting dose 3-6 mg/kg Q24
  - One week later
    - UCCR
      - Normal = q24
      - Elevated = q12
    - ACTH stim
      - 1-5 ug/dl
Trilostane

• 2011
  • Dose
    • 1 mg/kg q12
    • Often have to get medication compounded
  • ACTH stim
    • Day 7-10
    • Post 4-9 ug/dl
• More subjective range
  • Owner observations
  • Clinical signs
• Protocols likely to become more refined over the coming years

• Efficacy with PDH
  • 85%
  • Similar to lysodren

• Side effects
  • 25% Addisonian
  • Some permanent
  • Vomiting
  • Diarrhea
  • Lethargy
  • Similar to lysodren

• With therapy
  • Adrenals enlarge
    • Continued stimulation by pituitary
    • Smaller with lysodren
  • True destruction of the gland

• AT
  • Few studies have suggested improved survival with trilostane vs lysodren
    • Controls clinical signs of HAC
    • Not growth of the mass
    • Less toxicity
  • May also be better choice in medical therapy for cats

Ketoconazole

• Antifungal medication
  • Inhibits cortisol production
  • 11-hydroxylase
  • Very expensive
  • Only efficacious in approximately 50% of dogs

• Side effects:
  • GI
  • Hepatic
  • Glucocorticoid insufficiency
  • Interferes with metabolism of other medications
  • Not commonly used
L-deprenyl (selegeline, Anipryl®)

- Is FDA approved for canine HAC
- Mechanism
  - monoamine oxidase B inhibitor
  - increases neuronal dopamine

L-deprenyl (selegeline, Anipryl®)

- Increases dopamine production
  - Prevents ACTH release from pars intermedia only
  - No effect on pars distalis
- Efficacy
  - 20% (?)
- No biochemical tests for monitoring therapy
  - Subjective only

L-deprenyl (selegeline, Anipryl®)

- Side effects:
  - Uncommon
    - Vomiting
    - Diarrhea
    - Listlessness
    - Disorientation
    - Decreased hearing

Metyrapone (Metopirone®)

- Inhibits cortisol synthesis
- Used only in cats for control prior to sx
- Not currently available

Surgery

- Treatment of choice in cats
  - PDH – bilateral adrenalectomy
    - Trilostane?
  - AT – unilateral adrenalectomy
  - Very high complication rate

Surgery

- Hypophysectomy
  - Removal of pituitary gland
  - 150 dogs
  - 68% 4 year survival rate
    - Medical therapy
      - Diabetes insipidus
      - Hypothyroidism
Surgery

- Adrenal surgery in dogs
  - Adrenal tumors less responsive to medical therapy
  - Complication rate
    - Up to 50%
    - Pancreatitis
    - Addison’s
    - PTE
  - Mortality rate
    - 22-29%

Pituitary macroadenoma

- Radation therapy
  - Treatment of choice
    - Pituitary > 8 mm in height
  - Avg survival
    - 18 months
  - Primary prognostic factor
    - Degree of neuro signs prior

Atypical Cushing’s

- Very controversial disease
- Increased sex hormone production
  - Progesterone
  - Estrogen
  - Testosterone
- Clinical signs consistent with Cushing’s
  - Normal cortisol levels

Atypical Cushing’s

- U of Tenn
  - Adrenal panel
- Therapy
  - Melatonin
  - Lignans
  - Maintenance lysodren

Questions?