ETIOLOGIES

Pituitary-induced bilateral adrenocortical hyperplasia also known as pituitary-dependent Cushing's disease (PDH) accounts for about 85% of all cases of spontaneous hypercortisolism in the dog. It results from either an adenohypophyseal ACTH-secreting micro- or macroadenoma or from excess pituitary ACTH secretion due to oversecretion of corticotrophin releasing factor (CRF) by the hypothalamus. The end result of both processes is hypersecretion of ACTH causing bilateral adrenocortical hyperplasia and subsequent hypercortisolism.

Adrenal tumors consist of either functional adenomas or adenocarcinomas of the adrenal cortex. These comprise 10-15% of all causes of spontaneous Cushing's syndrome in dogs.

Iatrogenic hypercortisolism is by far the most common cause of the "Cushingoid" dog. It is caused by overtreatment with glucocorticoid drugs (including Florinef).

BREEDS, AGE, SEX

Endogenous Cushing's disease is commonly reported in poodles, dachshunds, and terriers. It can be seen in any breed and mixed breeds as well. The average reported age is 8 years, but can range from very young (3 years) to very old (>12 years). There is no particular sex predilection.

CLINICAL SIGNS

1. Polydipsia and polyuria (PD/PU) are very common complaints. The hypothetical mechanisms include: (1) increased renal free water clearance as a result of increased renal blood flow and (2) inhibition of ADH release and its effect on the renal collecting ducts. A small percentage of dogs (10%) do not show PD and PU.

2. Polyphagia is a very common sign. It may be the main complaint along with a tendency toward obesity. The cause is unknown.

3. Pendulous abdomen has a high incidence. It results from abdominal muscle weakness, hepatomegaly and intraperitoneal fat deposition and is commonly mistaken for ascites.

4. Bilateral symmetrical alopecia typically has trunkal distribution and results from atrophy of the pilosebaceous apparatus. There is a variable incidence of skin pathology while a number of dogs do not have any changes whatsoever.

5. Other skin abnormalities include hyperpigmentation, comedone formation, thin skin (especially noted in inguinal area), calcinosis cutis (dry or inflammatory forms), tendency toward ecchymosis following venipuncture and superficial bacterial skin infections. Chronic demodicosis can also occur.

6. Hepatomegaly is due to steroid hepatopathy as a result of hepatic glycogen
deposition. It does not usually cause significant hepatic dysfunction, however.

7. **Anestrus and testicular atrophy** probably result from inhibition of gonadotropin release.

8. **Muscle dysfunction and weakness - Myotonia** characterized with a stiff gait is a rare complication. Muscle weakness results from the generalized catabolic effects of hypercortisolism.

9. **Pulmonary calcification** is a rare complication associated with the dystrophic effects of prolonged hypercortisolism. Symptomatic severe respiratory impairment can result with PaO\(_2\) levels < 80 mmHg.

10. **Systemic hypertension** occurs in dogs with Cushing’s. Excess cortisol concentrations elevates plasma renin substrate, the circulating protein upon which renin acts to release angiotensin I. Therefore, the hypertension may be partly produced by angiotensin-mediated vasoconstriction.

11. **Central nervous system** signs of stupor, seizures, circling, ataxia, blindness, or Horner’s syndrome in a patient with HAC suggests an enlarging pituitary tumor which can be present in < 20% of dogs with PDH.

**THROMBOEMBOLISM**

Cushing’s syndrome is associated with a hypercoagulable state in both dogs and humans. One study (Jacoby RC, et al, Arch Surg, 2001 Sept; 136(9):1003-6) showed that levels of procoagulation factors II, V, VII, IX, X, XI, and fibrinogen were significantly increased in dogs with Cushing’s. In addition, the natural antithrombotic antithrombin was significantly decreased. Sites of involvement can include lungs, brain, bowel as well as others. Providing heparin during surgical procedures should be considered.

**CLINICOPATHOLOGICAL LABORATORY CHANGES**

The typical abnormalities are provided below:

1. **Hemogram** - Typical findings include mature neutrophilia, eosinopenia, and lymphopenia. Monocytosis and thrombocytosis can also occur. Polycythemia (PCV in low 50's) is sometimes present (due to 17-ketosteroid excess). Some dogs lack these hemogram changes.

2. **Serum liver enzyme elevation** - is usually characterized with an elevated alkaline phosphatase level (from steroid-induced hepatic isoenzyme induction). ALT, AST, and BSP retention can also be slightly to moderately elevated. Serum bilirubin and albumin levels are always normal in Cushing's although bile acid levels can be elevated.

3. **Glucose** varies from normal to overt diabetic range. Diabetes mellitus occurs in 10 to 20% of dogs with endogenous hypercortisolism.

4. **Plasma lipids** - hypercholesterolemia and hypertriglyceridemia can occur and cause
the blood to become lipemic.

5. Serum electrolytes are usually normal. Hypernatremia and hypokalemia are rarely seen.

6. **Urinalysis** - often dilute, but kidneys usually retain ability to concentrate. Bacteriuria due to lower urinary tract infection is common.

7. Glomerulonephropathy with proteinuria also occurs and may or may not resolve with treatment for Cushing’s. It is thought to be due to an antigen overload (R. Nelson, UCD). The urine protein-to-creatinine ratio is a simple test. Normal dogs show values < 1.0.

8. **Thyroid function** - usually normal despite low T3 and T4 blood levels. The latter is due to ability of cortisol to inhibit thyroid hormone protein binding. A normal TSH response test might be necessary to substantiate euthyroidism.

**IMAGING ABNORMALITIES**

There are several radiographic changes that characterize some dogs with Cushing's syndrome. These include: (1) soft tissue mineralization, that can involve skin, muscles, lungs, and blood vessels, (2) hepatomegaly and pendulous abdomen, and (3) osteoporosis, especially involving the vertebrae.

Approximately one-half of the adrenal adenomas and adenocarcinomas will calcify and subsequently be seen on plain abdominal radiographs. They are visualized cranial and slightly medial to the anterior pole of the kidneys (VD view especially important). An IVP (especially nephrogram phase) can "highlight" the tumor, but selective abdominal arteriography can be more specific. Remember to take thoracic radiographs in suspect neoplasia cases in order to detect pulmonary metastasis.

Abdominal ultrasound is now a commonly used diagnostic procedure where PDH characterizes as bilaterally enlarged adrenal cortices while adrenal tumors show one enlarged gland with a tumorous bulge with the contralateral gland being of normal size. Caution should be taken to avoid diagnosing bilateral nodular hyperplasia as neoplastic. Also note that ultrasound cannot distinguish between an adrenocortical mass and an adrenal medullary mass.

Abdominal MRI is a very informative imaging modality that provides the utmost of detail and visualization of special relationships.

**Do not forget to do thoracic radiographs if a malignancy is suspected.**

**ADRENAL FUNCTION TESTS**

Today, there is considerable controversy surrounding the optimal endocrinologic tests for diagnosing canine hyperadrenocorticism. The descriptions of these tests are provided:

A. **Urinary steroids** - requires a 24-hour urine collection and is, therefore, not very conducive for the practitioner. It is best to assay for 17-ketogenic steroids (normal: 1.13 to 3.67 mg/24 hours) or 17-hydroxycorticosteroids (average normal: 3.7 mg/m² per 24 hours).

B. **Basal plasma cortisol levels** - One basal value usually not dependable due to the
fluctuating and overlapping blood levels that occur in normal and cushingoid dogs. Normal unstressed dogs range between 1.9 to 2.5 micrograms/dl (by RIA). NOTE: values reported in nanograms/ml can be converted to micrograms/dl by moving the decimal point one place to the left.

C. ACTH stimulation test - assesses the adrenocortical response to exogenous adrenocorticotropic. It will accurately diagnose endogenous hyperadrenocorticism approximately 70-80% of the time, but will not distinguish between pituitary-induced Cushing's and functional adrenocortical tumors. Some functional adrenal tumors are autonomous and therefore do not hypersecrete cortisol subsequent to ACTH stimulation. However, recent findings show that approximately 50% will hypersecrete cortisol similar to pituitary-induced adrenal hyperplasia patients. Some adrenocortical tumors will respond minimally to ACTH stimulation. The post-stimulation cortisol levels can sometimes be as low as 2.0 to 3.0 μg/ml/dl. The reason for a tumor’s poor response include 1) the production of a different hormone such as 17-hydroxyprogesterone, 2) lack of receptors for ACTH, and 3) some aberrant biosynthetic pathway for cortisol synthesis.

D. The typical pituitary-induced Cushing dog will hypersecrete cortisol to levels in excess of 17.0 micrograms/dl following ACTH injection. There are some who respond to levels ranging 8 to 15 μg/dl, however. (A very low to minimal response to ACTH in a cushingoid dog suggests iatrogenic disease due to prior glucocorticoid treatments or adrenocortical tumor.)

E. Low-dose dexamethasone suppression test.

1. In the normal dog, dexamethasone will suppress pituitary ACTH secretion by negative feedback inhibition and thereby suppress adrenocortical cortisol secretion. This test is 90-95% reliable for diagnosing endogenous hypercortisolism.

2. Technique (from Peterson). Inject 0.01 mg/kg dexamethasone phosphate IM or IV and collect plasma cortisol sample 8 hours later.

Dogs with spontaneous hyperadrenocorticism are usually resistant to low dose dexamethasone suppression (i.e., they have "inadequate suppression."). The test is approximately 94% accurate in distinguishing normal from spontaneously hyperadrenal dogs. In 80% of dogs with adrenal-dependent and in 25% of dogs with pituitary-dependent hyperadrenocorticism, there is no suppression.

F. Hi-dose dexamethasone suppression test

1. Autonomous cortisol secreting adrenal tumors are independent of the ACTH inhibition caused by high doses of dexamethasone. On the other hand, dogs with pituitary-dependent hyperadrenocorticism ideally will show suppressed cortisol secretion subsequent to hi-dose dexamethasone-induced ACTH inhibition thereby differentiating the pituitary-induced form from functional adrenal tumors.

2. Interpretation: When using 0.1 mg/kg or 1.0 mg/kg dexamethasone (high dose), "adequate suppression" is defined as the serum cortisol decreasing to less than 50% of
the resting value. Most dogs with pituitary-dependent hyperadrenocorticism suppress adequately, whereas dogs with adrenal-dependent disease do not have adequate suppression. Therefore, if adequate suppression occurs, pituitary-dependent hyperadrenocorticism is diagnosed, but inadequate suppression is inconclusive because 25% of pituitary-dependent patients can fail to suppress, thus, making them indistinguishable from dogs with adrenocortical tumors. In these cases abdominal ultrasound examination will help to identify any adrenal mass.

G. Complete steroid profile

There are some atypical Cushing’s dogs that give normal cortisol results with the ACTH stimulation test, while simultaneously showing elevated levels of other steroid hormones. These “other” steroids include testosterone, estradiol, progesterone, and 17-hydroxy progesterone. The results of the adrenal steroid panel will not distinguish between PDH and AT (adrenal tumor). See Hill KE, et al, JAVMA 2005, 226:556-561.

The ACTH stimulation test is run according to routine protocol, but the test results provide an expanded steroid analysis. This test can be done at the University of Tennessee.