Hyperadrenocorticism Associated with Sex Steroid Excess

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Diagnosis of sex steroid excess or hyperadrenocorticism in dogs may be challenging. Unlike Cushing’s disease, sex steroid excess may have a multitude of manifestations that differ from standard hyperadrenocorticism. In particular, the clinical scenario of a dog with sex steroid imbalance involves one of three systems: dermatologic, reproductive, or hepatic. The history of a dog with hyperadrenocorticism manifesting as sex steroid imbalance often lacks the classical clinical signs of polydipsia and polyuria. Dogs with sex steroid imbalance will often be of specific breeds such as miniature poodles and exhibit trunkal hair loss as the only sign. There is often involvement of the reproductive system, manifested as the growth of perianal adenomas in neutered male or female dogs. The most common laboratory findings consist of elevations in serum alkaline phosphatase and serum alanine transferase. The following article reviews the etiology, common signalment, clinical signs, and laboratory findings associated with atypical hyperadrenocorticism caused by sex steroid imbalance and then explores the medical, surgical, and radiation treatment options.

KEYWORDS hyperadrenocorticism, Cushing’s syndrome, sex steroid excess, canine

Hyperadrenocorticism (HAC) may be divided into two broad categories. One category, pituitary-dependent hyperadrenocorticism (PDH), arises from adenomatous enlargement of the pituitary gland resulting in excessive adrenocorticotropic (ACTH) production. The other category, adrenal-dependent disease, is associated with functional adenomas or adrenocorticalomas of the adrenal gland. Although classical hyperadrenocorticism is most often caused by pituitary-dependent disease, sex steroid imbalance may be caused equally by adrenal hyperplasia, adrenal tumors (both malignant and benign), or pituitary-dependent HAC. Pure sex steroid excess is usually caused by adrenal disease rather than PDH.

Signalment

HAC is found in middle-aged to older dogs (7 to 12 years of age); approximately 85% have PDH, and 15% suffer from adrenal tumors. In contrast, sex steroid imbalance is caused equally by adrenal and pituitary tumors. Breeds in which PDH is commonly seen include the miniature poodle, dachshund, boxer, Boston terrier, and beagle; however, adrenal sex hormone alopecia is seen more frequently in miniature poodles, chow chows, Pomeranians, and arctic breeds such as Samoyeds, elkhounds, and Alaskan malamutes. Atypical or sex steroid excess HAC is more often caused by adrenal tumors (usually benign) compared with typical HAC.

History and Clinical Signs

The most common clinical signs associated with typical HAC are polydipsia, polyuria, polyphagia, heat intolerance, lethargy, abdominal enlargement or “pot belly,” panting, obesity, muscle weakness, and recurrent urinary tract infections. In contrast, dogs with sex steroid excess rarely exhibit polydipsia and polyuria because of the lack of hypercortisolemia; in fact, urine-specific gravity will often be high in dogs with this form of HAC. Although the pot-bellied appearance may be seen in dogs with sex steroid imbalance, it is not a common feature of the disease.

More commonly, dogs with sex steroid imbalance exhibit dermatologic manifestations of the disease as their only symptom. Dermatologic manifestations of canine HAC can include alopecia (especially trunkal), thin skin, phlebectasias, comedones, bruising, cutaneous hyperpigmentation, calcinosis cutis, pyoderma, dermal atrophy (especially around scars), secondary demodicosis, and seborrhea. On the other hand, dogs with adrenal sex hormone alopecia exhibit alopecia and hyperpigmentation without any other signs of typical HAC. Figure 1 shows a dog with typical dermatologic signs of HAC and Figure 2 shows a dog with adrenal sex hormone alopecia.

Reproductive signs of atypical HAC can include perianal adenoma in a female or castrated male, clitoral hypertrophy
in females, behavioral estrus in female dogs or cats, testicular atrophy in intact males, prostatomegaly in male castrated dogs, or behavioral and physical signs of testosterone excess (mounting behavior, penile barbs in cats). Abnormal patterns of sex steroid synthesis result in precursors of cortisol being generated from the adrenal cortex (Fig. 3). Often, particularly with adrenal tumors, there is preferential synthesis of precursors such as dihydroepiandrosterone, androstenedione, 17-hydroxyprogesterone, and pregnenolones, testosterone, estrogens, and progesterones may also be secreted in excess. The result is a wide variety of manifestations in target tissues that retain testosterone and estrogen or progesterone receptors. Clinically the most common manifestation of sex steroid excess is the presence of a perianal adenoma in a neutered male or female dog. While this sign can be seen in dogs with conventional hyperadrenocorticism, it is uncommon and only occurs when sex steroid imbalance attends the Cushings syndrome.

Uncommon clinical manifestations of HAC in the dog can include such signs as hypertension, pulmonary thromboembolism, bronchial calcification or congestive heart failure, and neurologic signs, such as polyneuropathy/myopathy, behavior changes, blindness, or pseudomyotonia.\textsuperscript{12,13} Evidence of hypercortisolemia may be evident as weakening of collagen manifesting as cranial cruciate rupture (small dog) or corneal ulceration (nonhealing). Because these clinical signs are the result of increased cortisol, dogs with sex steroid imbalance often will not exhibit these manifestations.

**Laboratory Abnormalities**

In dogs, serum chemistry abnormalities associated with hypercortisolemia include increased serum alkaline phosphatase (ALP), increased alanine transaminase (ALT), hypercholesterolemia, hyperglycemia, and decreased blood urea nitrogen.\textsuperscript{14,15} The most common laboratory abnormality in dogs with sex steroid imbalance is increased ALP and ALT. In fact, this is the most common reason that dogs with this syndrome are presented to referral centers. Unexplained elevations of liver enzymes without hepatic symptomatology should prompt a search for sex steroid imbalance.

The hemogram is characterized by evidence of regeneration (erythrocytosis, nucleated red blood cells [NRBCs]) and a classic stress leukogram (eosinopenia, lymphopenia, and mature leukocytosis). Basophilia is occasionally observed.\textsuperscript{1,5,9} Many dogs with HAC show evidence of urinary tract infection without pyuria (positive culture), bacteriuria, and proteinuria resulting from glomerulosclerosis.\textsuperscript{1,5,13,16} As mentioned previously, dogs with sex steroid excess do not have loss of urinary concentrating ability nor do they exhibit an increased susceptibility to urinary tract infection.

Thyroid status is often affected in animals with HAC, as evidenced by decreased basal thyroxine (T\textsubscript{4}) and triiodothyronine (T\textsubscript{3}) caused by euthyroid sick syndrome and decreased endogenous thyroid-stimulating hormone (TSH) secretion caused by overcrowding of pituitary thyrotrophs.\textsuperscript{17} Dogs with PDH and sex steroid excess will often show the same changes in thyroid hormone status.

**Diagnostic Approach**

The diagnosis of HAC manifested as sex steroid excess should be based on appropriate clinical signs (first and foremost) followed by supporting minimum database abnormalities (high cholesterol, serum alkaline phosphatase [SAP], etc), and confirmed via an appropriate screening test for HAC.\textsuperscript{18,19} If screening test results are inconclusive (borderline, etc), or if laboratory abnormalities associated with HAC (increased SAP, etc) are noted in a dog without clinical signs of HAC, the dog should be retested at a later date (3 to 6 months) rather than be subjected to treatment for HAC without a definitive diagnosis. In particular, the diagnosis of sex steroid–induced Cushings disease may be especially difficult.

SAP isoenzyme is a screening test available to the practitioner. The advantages of SAP isoenzyme measurement are wide availability and low cost\textsuperscript{20-23}; however, even small elevations in serum cortisol, such as those that occur with exogenous steroid administration in ocular preparations, can induce SAP isoenzyme. This test has a very low specificity (<44%) because it is affected by stress and by nonadrenal disease. Additionally, this test cannot differentiate between endogenous and iatrogenic HAC.

The urine cortisol-to-creatinine ratio (UCCR) is highly sensitive in separating normal dogs from those with HAC, but the test is not highly specific for HAC because dogs with
moderate to severe nonadrenal illness also exhibit elevated ratios. Therefore, UCCRs should be determined based on free-catch urine collected at home by the client. Even the stress of transporting the dog to the veterinarian’s office, the stress of cystocentesis, or both can be enough to cause a falsely elevated UCCR. An elevated UCCR should be confirmed with an ACTH stimulation test, an intravenous low-dose dexamethasone suppression (LDDS) test, or an oral LDDS test. False-negative tests for hyperadrenocorticism using the UCCR are common in dogs with sex steroid imbalance particularly if they are secreting only sex steroids.

The LDDS is usually considered the screening test of choice for canine HAC when it is properly used; however, this test is inappropriate to document sex steroid imbalance. It is an extremely sensitive test (92 to 95%); only 5 to 8% of dogs with PDH exhibit suppressed cortisol concentrations at 8 hours (ie, 5 to 10% false negatives). In addition, 30% of dogs with PDH exhibit suppression at 3 or 4 hours followed by “escape” of suppression at 8 hours; this pattern is diagnostic for PDH, making further testing unnecessary. The major disadvantage of the LDDS test is the lack of specificity in dogs with nonadrenal illness. Kaplan and coworkers recently reported that more than 50% of dogs with nonadrenal illness will have a positive LDDS test. It is recommended that a dog be allowed to recover from the nonadrenal illness before testing for HAC with a LDDS test. Unfortunately, dogs that suffer from atypical HAC will not have elevations in serum cortisol and hence will show suppression on the LDDS; therefore, this test is not recommended for diagnosis of atypical HAC.

The ACTH stimulation test is used to diagnose a variety of adrenopathic disorders, including endogenous or iatrogenic HAC and spontaneous HAC. As a screening test for the diagnosis of naturally occurring HAC, the ACTH response test has a diagnostic sensitivity of approximately 80 to 85% and a higher specificity than the LDDS test. In the study by Kaplan and coworkers, only 15% of dogs with nonadrenal disease exhibited an exaggerated response to ACTH stimulation.

Dogs suffering from adrenal sex steroid excess may have negative ACTH stimulation and LDDS tests because serum cortisol concentrations are normal. This may be due to excess cortisol precursors. Increases in progesterone, 17-OH-progesterone, androstenedione, testosterone, and estrogens may require dynamic adrenal testing using the ACTH stimulation test and measurement of sex steroids in addition to cortisol. The ACTH stimulation test with measurement of steroid precursors, particularly 17-OH-progesterone, is the test of choice to document sex steroid excess.

Differentiating PDH from Adrenal Disease

After the diagnosis of HAC has been confirmed, differentiation of pituitary-dependent versus adrenal-dependent disease may be necessary. Although the majority of dogs with HAC suffer from PDH, the presence of atypical HAC should alert the clinician to the fact that a differentiation test is appropriate.

Measurement of endogenous plasma ACTH concentrations is the most reliable method of discriminating between PDH and adrenal tumor. Dogs with adrenal tumors have low to undetectable ACTH concentrations; in contrast, dogs with PDH exhibit normal to elevated ACTH concentrations. Recently, researchers have found that the addition of the protease inhibitor, aprotinin, to whole blood in EDTA tubes inhibits the degradation of ACTH. Samples may be collected, spun in a nonrefrigerated centrifuge, and kept for up to 4 days at <4°C. Dogs with adrenal tumors have low to undetectable ACTH concentrations; in contrast, dogs with PDH exhibit normal to elevated ACTH concentrations.

Diagnostic imaging of the pituitary and the adrenal glands can be accomplished via abdominal radiography, ultrasonog-
raphy, computed tomography, or magnetic resonance imaging. Abdominal radiographs should be performed in all dogs; approximately 30 to 50% of dogs with adrenal tumors exhibit a mineralized mass in the area of the adrenal glands. A more sensitive method of identifying adrenal tumors is via abdominal ultrasonography. Dogs with typical HAC from PDH will show bilateral adrenal enlargement, while those with adrenal tumors will have unilateral adrenal enlargement with contralateral adrenal atrophy. Specifically, dogs with sex steroid excess often will have nodules on one or both adrenals, without contralateral adrenal atrophy. In addition, liver metastasis or invasion into the vena cava may be demonstrated in dogs with adrenal carcinomas. Either computed tomography or magnetic resonance imaging, or both, of the brain or abdominal cavity in dogs that fail to suppress on the HDDS may demonstrate unilateral adrenal enlargement (50%), pituitary macroadenoma (25%), or pituitary microadenoma (25%).

Treatment—Adrenal Sex Steroid Excess

Three treatment options are available for canine HAC. Medical, surgical, and radiation therapy have all been used, and all three treatment modalities have met with varying degrees of success.

Mitotane

Medical therapy has been successful in most dogs with either typical or atypical hypoadrenocorticism. The majority of dogs respond to mitotane (Lysodren (o,p-DDD)–Bristol-Myers Squibb) (Fig. 4). An outline for the standard treatment of Cushing’s syndrome with mitotane is shown in Figure 5. Other methods of treatment with mitotane include creating hypoadrenocorticism by administration of 50 mg/kg/d for 30 days and administration of a low dose (25 mg/kg) weekly for 1 month. Monitoring consists of performing ACTH response tests every few weeks and then every 3 to 4 months; the post-ACTH cortisol level should be in the normal range.

Ketoconazole

Ketoconazole (Nizoral; Jannsen Pharmaceutica, Titusville, NJ) is a steroid inhibitor used to reversibly treat dogs with HAC. A dosage of 15 mg/kg/d divided into twice-daily dosing is used initially, and the dose is increased slowly (over 3 weeks) to 30 mg/kg/d divided to twice daily dosing. Ketoconazole is not often used in dogs because of expense and because severe anorexia may result from the drug itself. The primary use of ketoconazole in HAC is to prepare the dog for surgical adrenalectomy or radiation therapy. Cortisol levels after ACTH stimulation should be in the normal range.

Deprenyl

There are no large studies looking at the efficacy of deprenyl (selegiline; Anipryl–Pfizer Animal Health) in dogs with PDH compared with placebo. As a monoamine oxidase type B (MAO-B) inhibitor, deprenyl would be expected to work on
the minority of dogs with PDH and suffering from pars intermedia tumors because these tumors are thought to be under the regulation of dopamine. I limit the use of this drug to patients with mild HAC (skin disease only) or patients that do not tolerate mitotane or ketoconazole.

**Trilostane**

Trilostane (Vetoryl; Arnolds Pharmaceuticals, UK) is an orally administered competitive inhibitor of 3-beta-hydroxysteroid dehydrogenase, the enzyme that mediates the conversion of pregnenolone to progesterone and, hence, its end-products (cortisol, aldosterone, and androstenedione) in the adrenals. Studies in dogs with HAC have shown that trilostane is an effective steroid inhibitor that is associated with minimal side effects.43-45 Although currently unavailable in the United States, trilostane may prove to be a reasonable alternative to mitotane therapy for HAC in dogs, particularly those suffering from sex steroid imbalance.

**Surgical Therapy**

Surgical treatment of HAC consists of unilateral adrenalectomy. The reader is referred to surgical texts for an explanation of the surgical procedure; however, medical management of the dog during the operative and postoperative period is essential for a good outcome. Glucocorticoid (prednisone orally at 0.2 mg/kg daily) supplementation should be initiated immediately before adrenalectomy to prevent corticosteroid withdrawal syndrome. Complications following adrenalectomy include dehiscence, poor wound healing, Adisonian crises, and enlargement of the pituitary tumor, which may result in blindness or seizures (Nelson's syndrome).

**Radiation Therapy**

Because approximately 85% of all dogs with typical HAC have PDH, radiation therapy is another treatment option for many patients; however, radiation therapy is expensive ($1500 to $2000) and time-consuming (3 weeks' duration). Radiation therapy is an effective method of treatment and is associated with low morbidity, but signs of PDH may take several months to subside in treated animals. Eventually, treated dogs do well long term (years) because the primary disease process (pituitary tumor) has been addressed. Results of radiation therapy in dogs show that it is an effective method of treatment and is associated with low morbidity, but signs of PDH may take several months to subside in treated animals. Eventually treated dogs do well long term (years) because the primary disease process has been addressed.

**References**

42. Frank LA, Hnilica KA, Oliver JW: Adrenal steroid hormone concentrations in dogs with hair cycle arrest (Alopecia X) before and during treatment with melatonin and mitotane. Vet Dermatol 15(5):278-284, 2004