



CLINICAL KNOWLEDGE INSIGHTS

ENDOCRINE & METABOLIC DERMATOSES

HYPERADRENOCORTICISM – CANINE

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AT A GLANCE

- Hyperadrenocorticism (HAC) in the dog is a spontaneous disease arising most commonly from a corticotropin secreting, pituitary adenoma that results in bilateral adrenal gland hyperplasia and excessive production of cortisol [pituitary dependent form of HAC (PDH)]. Hyperadrenocorticism can also occur as a result of a cortisol secreting adrenal tumor or adrenal dependent HAC.
- Hypercortisolemia also develops when dogs are administered excessive exogenous sources of glucocorticoids in the management of immune mediated disease or hypersensitivities. Iatrogenic hypercortisolemia is not synonymous with HAC. However all causes of hypercortisolemia can be correctly referred to as Cushing's syndrome¹.
- The skin is particularly sensitive to increases in cortisol and a number of characteristic changes can occur because of both the protein catabolic and antimitotic effects of glucocorticoids. Glucocorticoids cause cornification abnormalities, inhibit both fibroblast proliferation and collagen

production, and cause pilosebaceous gland atrophy. These changes can account for many of the cutaneous clinical signs seen in dogs with HAC.

WHAT DOES IT LOOK LIKE?

- Middle aged to older dogs (median age at time of diagnosis is 10 yrs)². Dogs with adrenal dependent HAC are typically older than those with PDH; 75% of PDH and 90% of dogs with adrenocortical tumors are > 9 years of age at time of diagnosis^{1,3}.
- Typically HAC is diagnosed in small breed dogs and 75% are less than 20 Kg in body weight^{1,3}. However, 50% of dogs with adrenal dependent HAC are greater than 20 kg. Poodles, Dachshunds, Boxers and a number of terrier breeds are predisposed to develop PDH³.
- The most common cutaneous clinical sign seen is alopecia. Non-cutaneous clinical signs are typically also present in dogs with HAC. Commonly seen clinical signs include polyuria and polydipsia, polyphagia, a pendulous abdomen due to muscle wasting, hepatomegaly, muscle weakness and/or atrophy, reproductive changes (anestrus in intact female dogs, clitoral hypertrophy and testicular atrophy), panting, hypertension and peripheral neuropathies (facial paralysis). In some cases, skin changes may be the first presenting clinical sign leading to the diagnosis of HAC without other more typical clinical signs being present⁴.
- Alopecia often begins over pressure points and most often involves the trunk in a bilaterally symmetric distribution, but it can present as generalized hair thinning or patchy truncal alopecia.
- The persisting hair coat is often dry, brittle and can be either dull or faded in color reflecting persistence of hair follicles in telogen and a failure to have anagen initiated. This can also explain failure of clipped hair to regrow as quickly.
- Hypercortisolemia (endogenous or exogenous) results in thin, hypotonic skin that is easily bruised. This thin hypotonic skin is most evident on the ventral abdomen where atrophy of dermal collagen makes dermal vasculature easily visible.
- Hyperpigmentation, cornification disturbances (seborrhea), phlebectasias (dilations or varicosities of the small venules in the superficial dermis), comedones (plug of keratin and sebum within a hair follicle that is blackened at the surface), milia (white, keratin filled with no opening to the skin surface) and striae (irregular areas of skin that look like bands or lines) are all skin changes that can occur as a result of hypercortisolemia⁵.
- Delayed wound healing and increased risk for infections are also consequences of hypercortisolemic changes to the skin
- Bacterial and fungal skin infections can develop in dogs with hypercortisolemia.
- Calcinosis cutis is a dystrophic calcification seen in dogs with endogenous or exogenous hypercortisolemia. Labrador Retrievers, Rottweilers, Boxers and Pit Bull Terriers were overrepresented breeds in one study⁶. That same study showed the mineral present within the calcinosis cutis lesions to be apatite crystals⁶. Lesions of calcinosis cutis often progress to coalesce into firm, gritty plaques that may ulcerate and develop hemorrhagic crusts. Clinically these lesions most often develop over the dorsum or in the inguinal area.⁶ Dystrophic calcification can also involve mucosal membranes and the tongue.

PATHOLOGIC IMAGE LIBRARY : HYPERADRENOCORTICISM - CANINE



Adrenal dependent HAC (Labrador retriever) - resultant dry, dull hair coat; alopecia over elbow pressure points/lumbar region; pendulous abdomen; sway back posture



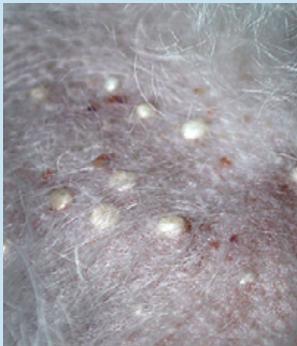
Marked temporal muscle atrophy (same dog as left) and focal alopecia peri-ocularly. Demodex mites found from deep skin scrapings of facial alopecia lesions.



Border terrier - thinning hair coat, multifocal patchy truncal alopecia, & hyperpigmentation. Alopecia present over pressure points & dorsal aspect of tail.



Prominent abdominal distension; skin thinning - visible superficial vasculature; numerous comedones; erythema, papules from secondary bacterial skin infection



Milia are present on the dorsum of a Bichon Frise with HAC



Evident abdominal distension, thin skin with bilaterally symmetrical areas of prominent vasculature and striae.



Calcinosis cutis lesions present inguinally in a dog receiving corticosteroids for management of immune mediated disease.



Resolution of the calcinosis cutis lesions after corticosteroids were discontinued and immune-mediated disease was managed with other medications.

All Photos are courtesy of University of California Davis, Veterinary Dermatology Service Clinical Photo Collection

WHAT ELSE LOOKS LIKE IT?

- Iatrogenic hypercortisolemia from exogenous parenteral and/or topical corticosteroid administration or application.
- Alopecia secondary to canine hypothyroidism
- Alopecia and hyperpigmentation secondary to sex hormone imbalances from testicular or adrenal neoplasia
- Hair cycle arrest in plush coated breeds (alopecia X, adrenal-like hyperplasia)

HOW DO I DIAGNOSE IT?

- Hyperadrenocorticism is diagnosed based on screening tests performed on dogs with compatible history and physical exam findings along with an awareness of any history of exogenous administration of corticosteroids and concurrent illnesses.
- If a complete blood cell count and a serum biochemistry panel are performed the index of clinical suspicion for HAC is increased if elevated liver enzymes are documented (particularly alkaline phosphatase which has a steroid induced isoenzyme). Other clinicopathologic abnormalities that may be seen in dogs with hypercortisolemia include leukocytosis with a mature neutrophilia, lymphopenia and eosinopenia; thrombocytosis; erythrocytosis; hypercholesterolemia; hypertriglyceridemia; hyperphosphatemia and a decreased blood urea nitrogen (BUN). Diabetes mellitus may occur concurrently with HAC and if concurrently present it is typically difficult to control.
- Urinalysis often documents a urine specific gravity that is below 1.020. Proteinuria with a mildly elevated urine protein to creatinine ratio may be present. Urinary tract infections are common and a urine sediment exam may document bacteruria without concurrent pyuria.
- Diagnostic imaging may include radiography, abdominal ultrasound or advanced imaging such as computed tomography (CT) or magnetic resonance imaging (MRI). Abdominal radiographic changes include hepatomegaly and possibly calcification of an adrenal mass (about 50% of adrenal adenomas or carcinomas have some degree of calcification)⁷. Abdominal ultrasound may reveal bilateral or unilateral adrenomegaly. Rarely bilateral adrenomegaly is documented with a concurrent adrenal mass. Presence of bilateral adrenomegaly without an adrenal mass can differentiate PDH from an adrenal tumor causing HAC. Computed tomography or MRI are both used to image adrenal glands. MRI is also used in evaluation for possible macroadenomas of the pituitary gland.
- Endocrine function testing to evaluate for HAC involves using one or more screening tests and if positive then differentiating the cause of HAC. Screening tests include a urinary cortisol to creatinine ratio (UCCR), an ACTH stimulation test or a low dose dexamethasone suppression test (LDDST).
- The sample for a UCCR should be obtained in the morning preferably in the dog's home environment. The test is highly sensitive but has low specificity as numerous other diseases can increase the UCCR. The UCCR is most valuable in ruling out the diagnosis of HAC because a normal result is not compatible with a diagnosis of HAC.

- An ACTH stimulation test measures the adrenal glands response to a maximal dose of ACTH. There are several different protocols depending on the form of ACTH used and readers are referred to veterinary internal medicine textbooks. Compared to the LDDST the ACTH stimulation test has a couple of disadvantages: it is less sensitive, more expensive and it cannot differentiate PDH from adrenal tumor causing HAC. It can however differentiate iatrogenic hypercortisolemia from HAC, may allow evaluation of other adrenal hormones in patients where disturbances in other adrenal steroid hormones are suspected and it is a shorter test to perform than the LDDST.
- The LDDST is typically considered the preferred screening test to diagnose HAC in the dog as it is much more sensitive than the ACTH stimulation test but it cannot identify cases of iatrogenic hypercortisolemia. The specificity of this test is however low and nonadrenal illness may alter the LDDST results. If a dog has cortisol suppression at 4hrs on a LDDST which then normalizes at 8 hrs this is diagnostic for PDH and further differentiating testing is not required. However not all dogs with PDH have suppressed cortisol at 4 hrs and in those cases where there is partial to no suppression additional diagnostic tests are needed to differentiate PDH from an adrenal tumor causing HAC.
- HAC caused by PDH vs. an adrenal tumor may be differentiated based on the LDDST results and if not possible, results of abdominal ultrasound, performing a high dose dexamethasone suppression test (HDDST) or measuring endogenous ACTH may help differentiate the cause of HAC

HOW DO I MANAGE IT?

- The cutaneous changes associated with hypercortisolemia will persist or progress unless the hypercortisolemia can be corrected. Iatrogenic hypercortisolemia should be managed by reducing the use of exogenous corticosteroids in an affected dog.
- Dogs should only be treated for HAC when there are compatible clinical signs and endocrine function tests are diagnostic for HAC. Dogs with chronic skin disease that is clinically compatible with HAC should not be empirically treated without confirmatory endocrine function testing. Likewise, dogs with suggestive diagnostic test results but no compatible clinical signs should not be treated.
- Currently, HAC is most often managed with trilostane (Vetoryl®, Dechra Ltd) which is the only FDA approved drug for the treatment of both pituitary and adrenal dependent HAC.
- Trilostane works to reduce hypercortisolemia through competitive inhibition of the adrenal gland enzyme 3- β -hydroxysteroid dehydrogenase thus inhibiting adrenal gland steroidogenesis and the production of cortisol.
- The dose is based on the most appropriate pill size for the dog's body weight based on a typical starting dose range from 2.2 to 6.7 mg/kg once a day. Treatment must be individualized and some dogs will be adequately controlled at a once daily dose of 3 to 6 mg/kg and others will be better controlled at a twice daily dosing of 1 to 2.5 mg/kg³.
- Trilostane should not be administered to dogs with primary hepatic disease or renal insufficiency. It should never be given to pregnant animals as it is shown to have teratogenic effects in laboratory animals. The most common adverse effects of trilostane include diminished appetite, vomiting, lethargy and weakness. More severe side effects are less common and include severe depression, hemorrhagic diarrhea, collapse, hypoadrenocortical crisis or adrenal necrosis/rupture leading to death. This last adverse effect is thought to be an indirect effect of trilostane and is hypothesized to result from the increase in adrenocorticotropic hormone (ACTH) during trilostane therapy⁸.

- Mitotane, o,p'DDD (Lysodren) was for many years the preferred treatment for HAC and it is still commonly used. The off label use of this drug to treat HAC is effective because of the selective adrenocortical necrosis and atrophy of the zona fasciculata (cortisol secreting layer of the adrenal cortex) and the zona reticularis (sex steroid hormone secreting layer of the adrenal cortex). The zona glomerulosa (mineralocorticoid secreting layer of the adrenal cortex) is less sensitive to the necrotizing effect of this drug but high doses can cause complete necrosis of all layers of the adrenal cortex. There are different published protocols and readers are referred to veterinary internal medicine textbooks.
- Mitotane adverse effects can develop during both induction and maintenance therapy and are most often associated with a deficiency in cortisol and patients improve when given glucocorticoid supplementation. In severe cases a hypoadrenocortical crisis with both glucocorticoid and mineralocorticoid deficiency occurring (Addisonian crisis) is possible.
- Other therapies that have been utilized in managing HAC include L-deprenyl, ketoconazole, radiation therapy of pituitary tumors, adrenalectomy or hypohysectomy. L-Deprenyl is FDA approved for management of mild cases of pituitary dependent HAC. It is a selective, irreversible monoamine oxidase inhibitor which results in increases in central dopamine concentrations which will have negative impact on corticotrophin release from the pars intermedia. However, fewer than 30% of dogs with HAC have a pituitary adenoma involving the pars intermedia so this treatment option has limited efficacy.
- All medical treatments involve careful monitoring of patients to determine that there is adequate control of the HAC without producing iatrogenic hypoadrenocorticism. This is done by evaluating success of treatment based on results of an ACTH stimulation test. When to perform the ACTH test and its interpretation will vary depending on the chosen medical management. There are many good internal medicine textbooks that can provide more detailed information in regards to the various treatment protocols.
- If pyoderma and/or otitis externa are present they should be managed with appropriate antimicrobial therapy based on cytology and bacterial culture and susceptibility testing.

COMMENTS

- Lesions of calcinosis cutis typically resolve in time if the hypercortisolemia can be resolved or managed. In some cases osseous metaplasia can occur. The resulting osteoma cutis lesions will not regress.
- Dimethyl sulfoxide (DMSO) gel has been reported to be of some benefit in hastening the resolution of calcinosis cutis lesions when applied once to twice a day⁵. However the underlying disturbance of cortisol needs to be resolved or managed.
- It is important to remember that hypercortisolemia (endogenous or exogenous) can alter thyroid function. Dogs with hypercortisolemia will often have low or below reference range serum concentrations of total thyroxine and less frequently free thyroxine is also low³. Endogenous TSH in dogs with HAC is usually also low or normal. If a dog is presented with clinical signs such as alopecia, weight gain and hypercholesterolemia that could be compatible with either hypothyroidism or HAC, HAC should be screened for first before interpreting low thyroid hormone values.

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