Hyperadrenocorticism in Dogs

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Profile

Definition

- Hyperadrenocorticism (HAC) is caused by excess circulating cortisol or other steroid hormones.

Signalment

- Endogenous HAC occurs in middle-aged to older dogs.
  - Although the reported age range is 6 months to 20 years, almost all dogs with HAC are over 6 years of age.[1]
- Poodles, dachshunds, boxers, and various terrier breeds may have a greater risk of pituitary-dependent hyperadrenocorticism (PDH).[1]
- PDH occurs more frequently in smaller dogs, with 75% of dogs with PDH weighing <20 kg.[1]
- There is no sex predilection for PDH.
  - Female dogs may have increased risk for adrenal-dependent hyperadrenocorticism (ADH).[1]

Causes

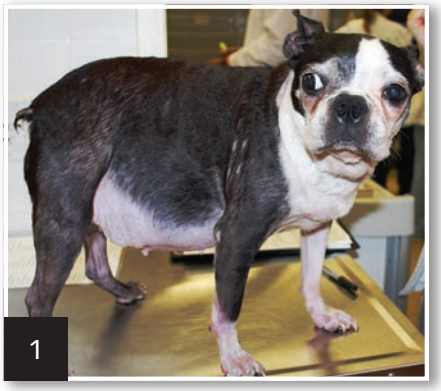
- Endogenous HAC is caused by an ACTH-secreting pituitary tumor (~85% of dogs) or a benign or malignant adrenal tumor (~15% of dogs).[1]
- Endogenous HAC may rarely be caused by ectopic ACTH secretion from a nonpituitary tumor[2] or food-dependent hypercortisolemia.[3]
- Iatrogenic HAC is caused by administration of exogenous glucocorticoids of any form.

History

- Polyuria (PU) and polydipsia (PD) are the most common complaints (~90% of HAC dogs).[1,4]
- Owners may note polyphagia, weight gain, and panting (50%–90% of dogs).[1,4]
- Alopecia is common (~60%–75% of affected dogs).[1,4]
- Lethargy may be noted and associated with muscle weakness, inability to rise.
- In dogs with a pituitary macroadenoma, owners may note behavioral changes (eg, disorientation, pacing, anorexia).

Physical Examination

- A distended or pendulous abdomen (pot-bellied appearance) is commonly noted (**Figure 1**).
  - Causes include abdominal muscular weakness, hepatomegaly, redistribution of fat, and urinary bladder distension.
- Dermatologic findings include alopecia, thinning of the skin, pyoderma, comedones, hyperpigmentation, and, less commonly, calcinosis cutis (**Figure 2**, next page).
- Muscle wasting may be present; pseudomyotonia is an uncommon finding, resulting in a stiff rear limb gait with a straight-legged appearance.
- Stupor or mental dullness may be noted in dogs with pituitary macroadenomas.



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Typical pot-belly appearance and generalized thinning of hair in a dog with pituitary-dependent hyperadrenocorticism.

Diagnosis

Definitive Diagnosis

- HAC diagnosis depends on consistent clinical signs and laboratory findings, exclusion of exogenous administration of glucocorticoids, and testing of adrenal function.
- Adrenal function tests for HAC can be separated into screening and differentiating tests.

Screening Tests

- Screening tests are used to confirm HAC; results can be considered as consistent with or not consistent with diagnosis.
  - If results are not consistent with HAC, but clinical suspicion is high, a different screening test should be pursued or testing

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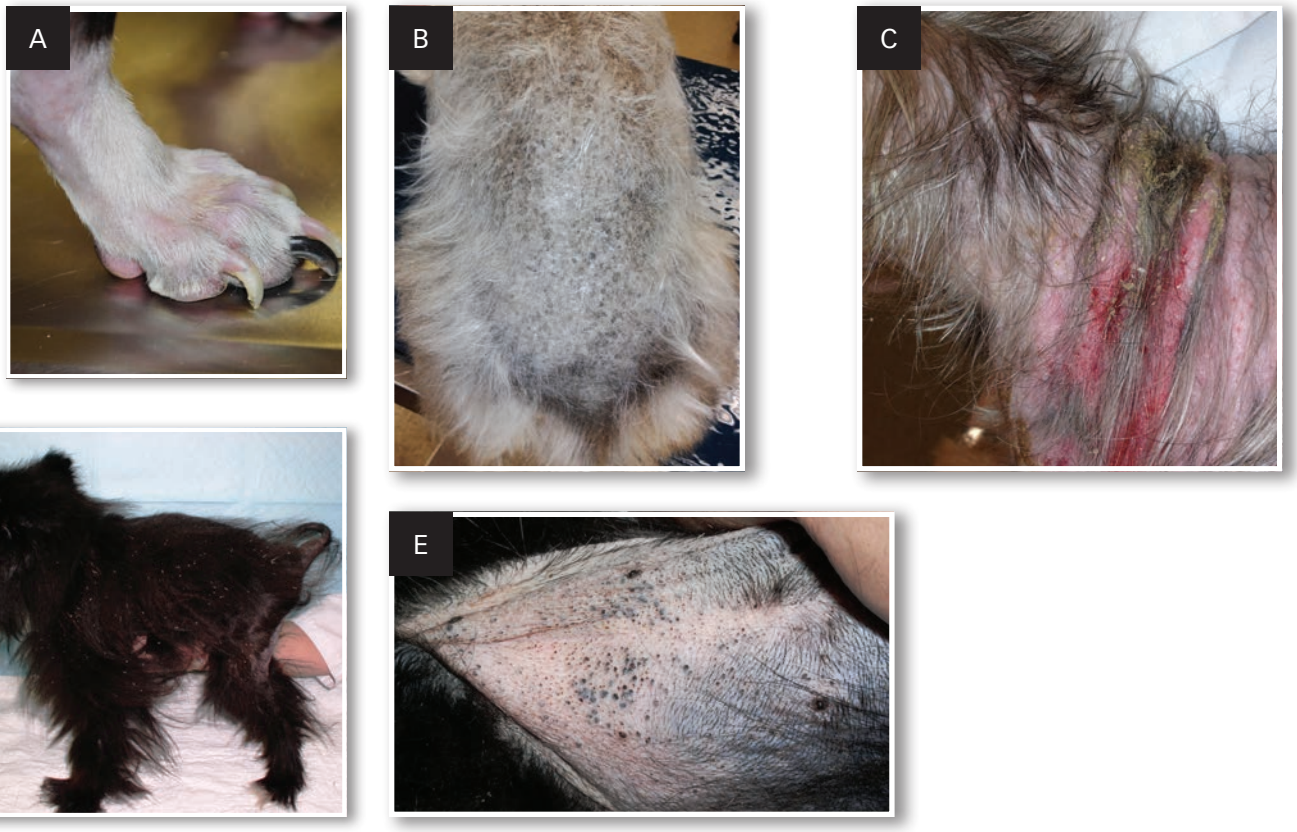
ACTH = adrenocorticotropic hormone, HAC = hyperadrenocorticism, PD = polydipsia, PDH = pituitary-dependent hyperadrenocorticism, PU = polyuria

2 **Dermatologic manifestations that contribute to HAC suspicion: Close up view of the alopecia of the distal limb and foot (A). Typical dorsal trunk alopecia in a dog with PDH (B). Skin lesions on the cervical region are consistent with calcinosis cutis (C). Alopecia and thinning hair on the caudal aspects of the rear legs and the tail in a dog with PDH. The dog also has moderate muscle atrophy (D). Comedones on the ventral abdomen (E).**



repeated in 3–6 months if initial clinical signs are mild.
- ❏ Testing should be postponed if significant concurrent illness is present.

- Urine cortisol:creatinine ratio has good sensitivity (90%–100%) but poor specificity (20%–40%).[5-7]
  - ❏ This can be used for screening when clinical suspicion is low but HAC is considered in the differential.
  - ❏ A first-morning urine sample collected 2–3 days or more after clinic visit or other stressful event is recommended.
- Low-dose dexamethasone suppression (LDDS) test has reported sensitivity and specificity of 85%–100% and 44%–73%, respectively.[7-10]
  - ❏ After obtaining blood for a baseline cortisol, dexamethasone (0.01–0.015 mg/kg) is administered IV and additional blood samples obtained at 4 and 8 hours for cortisol measurement.
  - ❏ This test may be the screening test of choice in dogs with endogenous HAC[11]; the author prefers this test for all dogs with suspected ADH.
- ACTH stimulation test has a reported sensitivity and specificity of 60%–85% and 60%–90%, respectively.[7,9,12-14]
  - ❏ This is the only test that can differentiate endogenous and iatrogenic HAC.
  - ❏ They should only be used once diagnosis has been established based on screening tests.
- Endogenous ACTH measurement should be low in dogs with ADH and high in dogs with PDH.
  - ❏ Because of the pulsatile release of ACTH, dogs with PDH may have ACTH concentrations within range.
  - ❏ ACTH degrades rapidly by plasma proteases. Appropriate sample handling is necessary for accurate results.
- LDDS test is unique in that it can serve as a screening and differentiating test if the 8-hour cortisol is higher than laboratory reference.
  - ❏ If the 4-hour cortisol is <50% of basal cortisol, the test is consistent with PDH.

Differentiating Tests

- Differentiating tests are used to determine if HAC is caused by PDH or ADH.

- If the 8-hour cortisol is <50% of basal cortisol but greater than the laboratory cut-off for normal suppression, the test may also be consistent with PDH.
- Lack of suppression could be caused by PDH or ADH.[15]

- High-dose dexamethasone suppression test is used if there is no suppression on the LDDS test.
  - If the cortisol at 4 or 8 hours is <50% of the basal cortisol, suppression has occurred and the test is consistent with PDH.
  - Approximately 25% of dogs with PDH will not suppress on either the low-dose or high-dose test and most dogs with ADH do not suppress.[15]
  - The author prefers using abdominal ultrasound rather than the high-dose test for differentiating PDH from ADH.

Laboratory Findings

- CBC: Common findings include a stress leukogram.
  - Thrombocytosis and, less commonly, mild erythrocytosis may be noted.
- Serum chemistry panel: Increased alkaline phosphatase activity is seen in most (~85%–90%) but not all dogs with HAC.
  - Alanine aminotransferase activity may be mildly increased.
  - Other findings include hyperlipidemia, fasting hyperglycemia, decreased blood urea nitrogen, and hypophosphatemia.
- Urinalysis: Urine specific gravity is commonly <1.020, but urine concentration can be variable.
  - Proteinuria is common.
  - Urinary tract infections are present in 40%–50% of dogs with HAC at initial diagnosis.[16]
  - Pyuria, stranguria, and hematuria may not be present because of antiinflammatory effects of cortisol.[1,4,6]
  - Urine culture should be performed.
  - In the absence of other evidence to treat (eg, pyelonephritis), these dogs should be monitored by urinalysis and clinical signs to determine if evidence of true infection occurs once HAC is controlled.

Imaging

- Thoracic radiographs: Mineralization of the trachea or bronchi is commonly present.
  - Radiographs should be evaluated for evidence of metastasis in dogs with ADH.
  - Pulmonary thromboembolism, although uncommon in dogs with HAC, may be seen.
- Abdominal radiographs: Hepatomegaly is seen in 80%–90% of dogs.
  - Approximately 50% of dogs with ADH will have adrenal glandular mineralization.
  - Calcium oxalate calculi may be found, and the author prefers abdominal radiographs to screen for uroliths, as ultrasound may miss stones in the ureters or urethra.
- The author prefers abdominal ultrasound to help differentiate PDH and ADH.
  - With PDH, adrenal glands are typically symmetrical and may be normal size or enlarged.
  - With ADH, there is commonly enlargement and loss of shape of 1 adrenal gland with atrophy of the contralateral gland.
    - In some cases, the contralateral gland size will be normal.
  - Ultrasound can be used to evaluate for vascular invasion or evidence of metastasis.
- The pituitary can be imaged with CT and MRI for evidence of a tumor.
  - MRI is more sensitive than CT.
    - Tumors >1 cm are more readily seen on CT.
  - Both modalities can be used to assess adrenal tumors and evidence of vascular invasion or metastasis.
  - The author typically recommends CT or MRI of the pituitary only when other tests are unable to differentiate PDH from ADH or if neurological signs of a macroadenoma are present.
    - If hypophysectomy or radiation is being considered, advanced imaging should be performed.

Tx Treatment

- Treatment for HAC should only be considered once a diagnosis has been established.
- The author does not recommend trial therapy to confirm diagnosis.
- The clinician should determine if treatment is indicated at diagnosis.
- Dogs that are nonclinical or only have mild signs (eg, increased ALP, hepatomegaly, mild alopecia) likely do not need treatment but can be monitored for progression of signs.
- Dogs with significant PU/PD, dermatological manifestations, or recurrent infections should be treated.
- Hypertension or proteinuria may warrant treatment of HAC, though anecdotally require specific treatment in addition to HAC treatment.

Medical

- Medical management is most commonly used for PDH but can be used for ADH if adrenalectomy is not an option.
- Trilostane and mitotane are used most commonly; both have similar

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efficacy in PDH and ADH treatment.

- Trilostane
  - Competitive inhibitor of 3-β-hydroxysteroid dehydrogenase
  - Reaches peak concentrations 2 hours after administration with return to baseline at 10–18 hours.
  - Administration with food enhances absorption
  - The manufacturer recommends a starting dose of 3–6 mg/kg PO q24h.
    - More recent studies have suggested better and faster control of signs with q12h administration, likely because of the duration of action being <13 hours in most dogs.
    - The author currently uses a starting dose of 1–2 mg/kg PO q12h.
  - Monitoring should include assessment of signs and ACTH stimulation testing 3–6 hours postadministration.
  - Time of testing should remain consistent; initial rechecks are 10–14 days and 30 days after start of therapy.
    - This ensures the initial dose is not causing hypoadrenocorticism.
    - If signs of HAC are not present or if financial constraints exist, the author omits this recheck.
    - At 30-day recheck, signs and an ACTH stimulation test should be evaluated.
  - If signs (PU/PD, polyphagia) are improved and the post-ACTH cortisol is between 3–8 µg/dL, the current dose is maintained and the dog is rechecked in 3 months.
  - If signs persist and the post-ACTH cortisol is >8 µg/dL, the dose is increased by 25%–50% and the dog rechecked in 2–4 weeks.
- Mitotane
  - Adrenocorticolytic agent predominately targeting the zonas fasciculata and reticularis
  - Treatment includes 2 phases: induction and maintenance.
  - Induction: Initial dose is 30–50 mg/kg PO per day, usually split q12h.
    - Dosage continues until the owner notes a decrease in signs (eg, slower to eat, decreased PU/PD) or a maximum of 7–10 days.
    - ACTH stimulation testing is repeated to assess therapy with the goal of a post-ACTH cortisol concentration being within the baseline cortisol reference range (ie, 1–5 µg/dL).
  - Maintenance: Total daily induction dose is used as the total weekly maintenance dose, typically split over 3–4 days per week.
    - Monitoring should include assessment of signs and ACTH stimulation testing 4 weeks after starting maintenance therapy, then as needed if dose adjustments are made or signs return.
  - The choice of drug is typically dependent on clinician preference and experience.
- Trilostane has similar adverse effects to mitotane but are typically less severe.
- For clients concerned about significant adverse effects, trilostane may be a better option.
- Trilostane can be more easily adjusted than mitotane in dogs in which control is lost (ie, change in dose versus reinduction).
- In large dogs, the author prefers mitotane because the long-term cost is usually less expensive.
- Owners may prefer the less frequent dosing of mitotane.

Surgical

- Adrenalectomy
  - First choice for ADH
  - Early studies indicated high peri- and postoperative mortality rates, but these have greatly improved.
    - In one study, vena caval invasion, particularly when extensive, was a significant risk factor for postoperative mortality.[17]
- Hypophysectomy
  - Can be used for treatment of PDH.
  - Most treatments have been performed in Europe but now are being offered in some U.S. facilities.
  - Appears to be an effective treatment with good long-term survival; dogs with pituitary tumors >10 mm have a shorter reported survival.[18]
  - Hypophysectomy may result in permanent or prolonged diabetes insipidus or secondary hypothyroidism caused by loss of ADH or thyroid-stimulating hormone production, respectively.

Client Education

- Treatment and monitoring of PDH can be expensive, especially in large-breed dogs.
- Once HAC is controlled, signs such as polyphagia and PU/PD usually resolve within 7–10 days.
  - Dermatologic changes may take months to resolve.
  - Liver enzymes may take longer to resolve and may never fully normalize.

Alternative Therapy

- Ketoconazole inhibits the synthesis of glucocorticoids and androgens and

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has been used for PDH or ADH treatment but has a much lower efficacy.
- L-deprenyl inhibits monoamine oxidase type B, resulting in increased dopamine concentrations in the pituitary and inhibiting secretion of ACTH from the pars intermedia.
  - Has poor efficacy and therefore is not recommended.
- Radiation therapy has been used in dogs with PDH and appears to improve neurologic signs associated with macroadenomas; it may not improve clinical signs of HAC.

In General

Relative Cost

- Medical therapy for PDH or ADH: $$$–$$$$
- Surgical therapy for PDH or ADH: $$$$$
- Radiation therapy for PDH: $$$$$

Cost Key
$ = up to $100
$$ = $101–$250
$$$ = $251–$500
$$$$ = $501–$1000
$$$$$ = more than $1000

Prognosis

- Prognosis for dogs with PDH treated medically is good with a reported median survival rate of 2 years based on a 1991 study.[19]
  - A more recent study found a survival rate of 900 days for dogs treated with twice daily trilostane versus 720 days for dogs treated with mitotane.[20]
  - In the author's experience, it is uncommon for dogs to die or be euthanized directly related to the consequences of HAC except for those with macroadenomas or in which PU/PD cannot be controlled.
  - Dogs with neurologic signs from a macroadenoma have a poorer prognosis but may do well with radiation therapy and medical treatment.[21]
- Prognosis for dogs with ADH is good to excellent with complete excision of adrenal tumors without metastasis.
  - Medical therapy for ADH has a fair to good prognosis with a median survival of 14–15 months recently reported.[22] ■ cb

See **Aids & Resources**, back page, for references & suggested reading.