

Pituitary Dependent Hyperadrenocorticism

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Spontaneous hyperadrenocorticism is a syndrome associated with chronic over production of cortisol by the adrenal cortices.^{1 2 3} Pituitary-dependent hyperadrenocorticism (PDH) is the most common form of spontaneous disease, accounting for 85% of the naturally occurring cases in dogs.^{1 2} It may also result from an adrenal tumor, and both types must be differentiated from iatrogenic hyperadrenocorticism.^{1 2 3} In some cases, concurrent pituitary-dependent hyperadrenocorticism and adrenal tumor may occur, and yield conflicting results in the diagnostic tests designed to differentiate them.^{4 5}

Signalment

Pituitary-dependent hyperadrenocorticism has been diagnosed in dogs ranging from 6 months to 20 years of age.¹ Most are more than six years of age. The median age at diagnosis is 11 years.² There is no sex predilection. All breeds can be affected, with Poodles, Dachshunds, Terrier breeds, Beagles, and German Shepherds being most commonly represented.^{1 2}

Clinical Signs

This is a slowly progressive syndrome that typically causes a gradual onset of clinical signs that may be attributed by the client to the aging process. While many organ systems may be affected, some dogs will only exhibit one or a few predominant clinical signs.^{1 2} Clinical signs can include polydipsia and polyuria, polyphagia, abdominal distension or “pot-bellied” appearance, and hepatomegaly. Hair coat changes, thin skin and coat, bilaterally symmetric truncal alopecia, secondary pyoderma and *Malassezia* dermatitis, comedones, hyperpigmentation, calcinosis cutis, and bruising may occur. Lethargy, muscle wasting of extremities, weakness, obesity, and decreased exercise or heat tolerance may be reported. Secondary urinary tract infection, secondary pancreatitis, anestrus, clitoral hypertrophy, or testicular atrophy may occur. Excessive panting is often reported, and in rare cases of secondary pulmonary thromboembolism, moderate to severe respiratory distress may be seen, and can be fatal.

When clinical signs and physical exam findings are consistent with hyperadrenocorticism, any recent corticosteroid administration should first be determined, including topical, eye, or ear preparations, as well as topical administration to other household pets to which the patient may be exposed.

Diagnostics

Based on physical exam and history alone, possible differential diagnoses may include hypothyroidism, diabetes mellitus, diabetes insipidus, liver disease, urinary tract disease, and a variety of dermatological conditions including pyoderma and *Malassezia* dermatitis. A minimum database that includes complete blood cell count (CBC), serum biochemistries, electrolytes, and urinalysis is essential in narrowing the list of possible differentials. Urine culture and sensitivity testing may also be indicated. These test results can confirm that pituitary-dependent hyperadrenocorticism should remain in the list of differential diagnoses, and can also help to identify concomitant medical problems, which should also be addressed. Endocrine testing is then required to confirm the diagnosis.^{1 6}

CBC abnormalities may include a stress leukogram and mild erythrocytosis. Serum chemistry changes often include elevations in serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and cholesterol. A mild hyperglycemia may be seen. Urine specific gravity is often < 1.020. In addition, proteinuria may be documented due to glomerular disease or urinary tract infection.^{1 2} Urine culture and sensitivity can reveal infection that may not be associated with hematuria or pyuria.

Thyroid function tests should be included in the diagnostic approach due to the overlap of clinical signs between hyperadrenocorticism and hypothyroidism.² Measurement of basal serum T3 and T4 concentrations may be insufficient because these levels may be decreased in 70% of dogs with spontaneous hyperadrenocorticism.²

Blood pressure evaluation is indicated when hyperadrenocorticism is suspected. More than 50% of affected patients are hypertensive. The hypertension typically resolves with successful management of the hyperadrenocorticism.²

Diagnostic imaging may be indicated and can include abdominal and thoracic radiographs, abdominal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI).^{1 2} Survey radiographs may identify hepatomegaly, mineralized bronchial walls, or pulmonary metastatic disease. Abdominal ultrasound can evaluate for concurrent disease such as uroliths, masses, or cysts. It can also evaluate the size and shape of the adrenal glands, which can help differentiate pituitary-dependent hyperadrenocorticism from adrenal tumor. If adrenal tumor is identified, the liver and caudal vena cava can be imaged sonographically to evaluate them for metastatic disease and tumor thrombus, respectively.^{1 2} Computed tomography (CT) and magnetic resonance imaging (MRI) are the most accurate and reliable methods of imaging the adrenal glands, and they can also be used to evaluate pituitary tumors. However, these procedures are not always readily available to the practitioner, and may be cost prohibitive to the client.

Liver biopsy is not a recommended screening test, but it may be performed as part of the work up. Hyperadrenocorticism is often associated with elevated liver enzymes and abnormal liver function tests typical of steroid-induced hepatopathy. If the index of suspicion is high for hyperadrenocorticism, this test is not recommended due to risk of infection or inadequate healing following biopsy.²

Pituitary-Adrenal Function Tests

Available pituitary-adrenal function tests include urine cortisol: creatinine ratio, low and high dose dexamethasone suppression tests, ACTH stimulation, and endogenous plasma ACTH concentration.^{1,2,6} Additional tests include plasma 17-hydroxyprogesterone concentration after ACTH stimulation, metyrapone suppression testing and corticotropin-releasing hormone stimulation testing, but are not yet routinely recommended.⁷

Misleading results of adrenal function testing may occur in the face of anticonvulsant medications, stress, and some non-adrenal illnesses including chronic kidney or liver disease and uncontrolled diabetes mellitus.^{2,6} Therefore, diagnosis should be made based on history, physical exam, and multiple tests that evaluate the hypothalamic-pituitary-adrenal axis.

The urine cortisol: creatinine ratio is a useful screening tool due to its sensitivity, but it has a low specificity.^{1,2,6} A normal value will exclude hyperadrenocorticism. However, a positive test must be confirmed with further endocrine testing.

The low dose dexamethasone suppression test evaluates the integrity of the negative feedback pathway of the hypothalamic-pituitary-adrenal axis.⁶ It has an overall sensitivity of 90-98% in detecting hyperadrenocorticism.^{1,2} Additionally, 25% of dogs with the pituitary-dependent form of the disease exhibit a characteristic “escape” pattern, which differentiates them from cortisol-secreting adrenal tumor. However, in most cases, it cannot distinguish between these two forms of disease.^{1,2}

The high dose dexamethasone suppression test also evaluates the integrity of the negative feedback pathway of the hypothalamic-pituitary-adrenal axis.⁶ It is used to differentiate between pituitary dependent hyperadrenocorticism and adrenocortical tumor once a diagnosis of hyperadrenocorticism has been made. Eighty per cent of patients with pituitary dependent hyperadrenocorticism will exhibit suppression. The 20% that do not suppress often have large pituitary tumors.¹ Inadequate suppression of cortisol with this test requires further testing to distinguish between pituitary-dependent hyperadrenocorticism and adrenocortical tumor.⁷

The ACTH stimulation test may be used to diagnose hyperadrenocorticism, differentiate between spontaneous and iatrogenic disease, and monitor response to treatment with mitotane.^{1,7} It evaluates the ability of the adrenal glands to secrete cortisol, and detects hypersecretion associated with spontaneous disease.^{2,6} It can detect 85-90% of dogs with pituitary-dependent hyperadrenocorticism, and 50% of dogs with adrenocortical tumors.¹ While it is less sensitive than other available screening tests, it has the highest specificity (82-91%).⁶ Therefore, as a screening test, it is most useful when the index for suspicion of hyperadrenocorticism is high. It cannot differentiate between pituitary-dependent disease and adrenal tumor.⁶

The endogenous plasma ACTH concentration may be used to distinguish between pituitary-dependent disease and adrenocortical tumor or iatrogenic disease.^{1,7} Adrenal tumor and iatrogenic hyperadrenocorticism suppress pituitary secretion of ACTH, while pituitary-dependent disease is caused by excess secretion of ACTH. Special sample handling is required and testing is available at only select laboratories.⁷ Results may be nondiagnostic in approximately 10 - 25% of cases.^{2,7}

Treatment Options

Treatment options for pituitary dependent hyperadrenocorticism include medical management with mitotane, ketoconazole, or selegiline, as well as radiation therapy.^{1,2,8} Surgical management has also been attempted experimentally using microsurgical transsphenoidal hypophysectomy.⁹

Mitotane Therapy

Mitotane (o,p'DDD) is the most common modality for treating canine pituitary-dependent hyperadrenocorticism.^{1,10} It causes selective adrenocortical necrosis in the zona fasciculata and zona reticularis. While it is considered cytotoxic, it appears to inhibit adrenocortical function without causing cell destruction, by mechanisms that are not fully understood. It may also have some effects on the zona glomerulosa, but it appears to have few clinically significant effects on aldosterone production. Oral absorption is enhanced by food, especially fat, so the medicine is best given with a meal. It has potentially severe toxic effects, so owners must be carefully instructed in safe handling of the medicine.¹¹

The goal of mitotane therapy is to induce a subclinical hypoadrenocortical state. The protocol involves two phases: induction and maintenance. Maintenance typically continues for life. The induction phase involves administering a daily loading dose to induce

remission. This phase normally lasts 7-10 days, but can take up to a few weeks in some patients. The dog should be monitored for the following signs of induction: decreased water intake, decreased appetite, lethargy, weakness, vomiting, or diarrhea.

Overdose can occur, inducing clinical hypoadrenocorticism, and can lead to a life-threatening situation. Some clinicians recommend administering concurrent low dose glucocorticoid supplementation with oral prednisone or prednisolone. However, others argue that this may mask signs of induction or overdose.¹⁰ If concurrent therapy is not used, the glucocorticoids are dispensed to the client in case of adverse effects, with instructions for use under veterinary supervision. If any of the above signs of induction occur, the mitotane is discontinued. If symptoms are significant, clients are instructed to begin corticosteroid supplementation at the above dosage.

Therapy is monitored with ACTH stimulation, which should be performed approximately 8-10 days after initiating treatment, or sooner if adverse effects develop.¹²¹¹ Cortisol levels should normalize within 2-4 weeks in most cases. If cortisol levels are above the normal basal range, the initial mitotane dose should be continued and ACTH stimulation should be performed at 5-10 day intervals until induction can be documented.¹¹

The maintenance phase is begun after induction has been reached. The chosen dose may depend on the clinician, the patient's condition, and on how rapidly the patient reached induction.¹¹⁰¹¹ If adverse effects develop at any time during therapy, mitotane administration should be discontinued and the patient evaluated with ACTH stimulation and serum electrolyte evaluation. Dosage amount and/or frequency may need to be adjusted based on response to therapy.¹¹

About 20-25% of patients will experience adverse effects at some time during therapy.¹ If electrolytes are normal, mitotane therapy can usually be resumed within 2-6 weeks. About 5% of patients will develop iatrogenic hypoadrenocorticism with hyponatremia and hyperkalemia.¹ These patients will require lifelong supplementation with mineralocorticoids. About 50% of patients will relapse within the first 12 months of therapy.¹ These patients generally require re-induction followed by a higher maintenance dose.

Patients should be monitored with ACTH stimulation after 3 and 6 months of maintenance therapy. Stable patients should be monitored every 6 months thereafter to monitor adrenal function and to guide mitotane dosage adjustments.

Non-selective adrenocorticolysis using mitotane has also been used, primarily in Europe, where mineralocorticoid replacement is less expensive than it is in North America. It may result in lower recurrence rates and longer survival times.¹² However, it also reduces the body's ability to adapt to stressful situations, which requires more vigilance on the part of the owner to recognize stressful situations so that glucocorticoid supplementation can be increased. It is probably more appropriate in the treatment of adrenal tumors, in which surgery is not an option.¹³

Ketoconazole Therapy

Ketoconazole is an alternative to mitotane for medical management of pituitary-dependent hyperadrenocorticism. It directly inhibits steroid synthesis by blocking several cytochrome P-450 enzyme systems.²¹⁴ Its effects on mineralocorticoids are negligible. The goal of therapy is to achieve subclinical hypoadrenocorticism based on ACTH stimulation testing. Once control is achieved, the medicine must be administered twice daily for life.

The disadvantages of ketoconazole therapy include its high cost, the need to administer the medicine twice daily for life, and a reported lack of efficacy of up to 50% of cases.¹¹⁰ Adverse effects can include vomiting, diarrhea, anorexia, lethargy, idiosyncratic hepatopathy, and thrombocytopenia.¹⁴

Selegiline Therapy

Selegiline is another alternative to mitotane for medical management of uncomplicated pituitary-dependent hyperadrenocorticism based on its indirect inhibition of cortisol production.¹⁵¹⁶ Selegiline is a selective monoamine oxidase (MAO) type B inhibitor. Since monoamine oxidase metabolizes dopamine, inhibition of MAO decreases dopamine breakdown. This allows dopamine levels to increase, which can in turn inhibit ACTH secretion by the pituitary gland. Decrease in pituitary ACTH secretion then decreases adrenal cortisol production.¹⁵ It is thought to improve behavioral abnormalities associated with hyperadrenocorticism.¹⁶

Response to therapy is evaluated based on physical exam and history. Low dose dexamethasone suppression results do not correlate with clinical efficacy of selegiline.¹⁵¹⁶ However, it is still recommended to monitor low dose dexamethasone suppression tests every 4-6 weeks to evaluate the pituitary-adrenal axis.

This therapy is not appropriate for patients with any other medical complications such as diabetes mellitus, pancreatitis, heart failure, kidney disease or other severe illness. It is not effective in treating cortisol-secreting adrenal tumors.¹ Reported efficacy rates in the treatment of pituitary-dependent disease varies from as high as 75-80% to as low as 20%.¹¹⁷¹⁸

Disadvantages of selegiline therapy include its high cost, the need to administer medicine daily for life, and variable reported efficacy. Adverse effects are uncommon (<5% of dogs), but include vomiting, diarrhea, restlessness, hyperactivity, agitation, insomnia, repetitive movements, lethargy, salivation, anorexia, decreased hearing or deafness, pruritus, licking, and shivers, trembles, and shakes.^{1 15 16} Drug interactions can occur, so it should not be administered with other monoamine oxidase inhibitors, opioids, or tricyclic antidepressants.^{15 16}

Radiation Therapy

Radiation therapy may be considered in dogs with pituitary macroadenoma or macroadenocarcinoma. Many of these cases have concurrent neurological signs caused by the space-occupying tumor. The severity of the neurological signs appears to be the strongest prognostic indicator.¹ Plasma ACTH and serum cortisol concentrations may not respond for weeks to months after treatment, so patients may need medical management for the hyperadrenocorticism in the interim. Disadvantages of radiation therapy for management of hyperadrenocorticism are its high cost and limited availability. Complications are related to adverse effects on surrounding brain tissue. Patients with severe neurological signs have a grave prognosis, so clients must understand the potential benefits and risks of the therapy.

Prognosis

Prognosis for hyperadrenocorticism is guarded due to the high risk of complications associated with the disease. These complications can include recurrence of clinical signs, pulmonary thromboembolism, infection, hypertension, congestive heart failure, progressive CNS disease associated with expanding pituitary tumor, glomerulopathy, and pancreatitis. Patients who succumb to these complications usually do so within the first 3-6 months after diagnosis.

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