COMPLICATIONS AND CONCURRENT DISEASE ASSOCIATED WITH CANINE HYPERADRENOCORTICISM

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Spontaneous canine hyperadrenocorticism (canine Cushing's syndrome) is a constellation of clinical signs and biochemical abnormalities that result from chronic exposure to elevated concentrations of glucocorticoids. Because of the multisystemic effects of long-term hypercortisolemia, dogs with Cushing's syndrome usually develop clinical signs that reflect dysfunction of many organ systems. In some dogs, however, one clinical sign may predominate. Sometimes the common clinical signs associated with hyperadrenocorticism may mask more serious problems. For example, the frequent clinical sign of polyuria and polydipsia may obscure other underlying or concurrent polyuric disorders such as pyelonephritis or diabetes mellitus. Although most dogs with hyperadrenocorticism appear healthy when examined, serious and life-threatening complications can occur secondarily to cortisol excess. Complications associated with hyperadrenocorticism include, but are not limited to, pyelonephritis, diabetes mellitus, systemic hypertension, pancreatitis, congestive heart failure, glomerulonephritis, pulmonary thromboembolism, advanced neurologic dysfunction secondary to large tumors of the pituitary gland, and iatrogenic glucocorticoid insufficiency after medical therapy with mitotane. These complications may occur insidiously over long periods of time or, in some cases, cause sudden death. General awareness, recognition, and treatment of complications associated with hyperadrenocorticism may improve the

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quality of life, decrease the severity of illness, and improve the prognosis (long-term survival) of dogs with this disorder.

COMPLICATIONS ASSOCIATED WITH MITOTANE THERAPY

Mitotane (o,p’-DDD) is the most frequently used drug in the treatment of canine hyperadrenocorticism. This drug can be used in the management of pituitary-dependent hyperadrenocorticism (PDH) or cortisol-secreting adrenal tumors. It decreases cortisol production by selective necrosis and atrophy of the adrenocortical zona fasciculata and zona reticularis. Because the zona glomerulosa is relatively resistant to the cytotoxic effects of mitotane, normal secretion of aldosterone is usually maintained.

Adverse effects to mitotane (overdosage), although usually not life threatening, should be anticipated when the drug is administered. The side effects most commonly observed are weakness, vomiting, anorexia, diarrhea, and ataxia. These adverse effects most often result from low or rapidly falling cortisol concentrations, or, less commonly, from direct drug toxicity. If adverse effects occur after administration of mitotane, assume until proven otherwise that the “drug reaction” is caused by low cortisol levels. The mitotane should be stopped immediately and glucocorticoids administered until the patient can be reevaluated. Direct toxicity to mitotane is usually associated with treatment of adrenocortical tumors, apparently because of the very high doses that are required to control clinical signs in some patients. If a direct toxic effect of mitotane is suspected, the dose is lowered by 25% to 50% after clinical signs of toxicity have resolved. Rarely, drug-induced central nervous system (CNS) signs occur. These adverse signs include ataxia, aimless wandering, circling, and head pressing. The drug-induced syndrome is transient, (lasting 12 to 48 hours) usually occurs after 3 to 24 months of therapy, and usually responds to giving lower doses more frequently.

In a retrospective study of 200 dogs with PDH treated with mitotane, 25% developed one or more side effects during the initial induction period, and 30% had adverse effects at some time during the maintenance phase of treatment. Most dogs show mild and transient signs with clinical improvement occurring 1 to 3 hours after receiving 5 to 10 mg of prednisone. A minority of dogs (2% to 5%) develop permanent Addison’s disease characterized by low basal and post-ACTH cortisol levels and electrolyte changes of hyponatremia and hyperkalemia. Occasionally, dogs may die of this complication, especially if the owner delays seeking veterinary attention. Adverse effects associated with mitotane can be prevented or reduced in severity (especially in the loading phase of therapy) if close veterinarian and client contact is maintained and attitude and appetite are used as behavior markers of mitotane overdose. Because most dogs with hyperadrenocorticism have excel-

EXACERBATION OF SUBCLINICAL DISEASE DURING THERAPY

Subclinical inflammatory or allergic disorders such as degenerative arthritis and flea-bite hypersensitivity are sometimes exacerbated during treatment with mitotane (or other therapy) for hyperadrenocorticism. Less commonly, dogs treated for hyperadrenocorticism develop immune-mediated or neoplastic disorders such as hemolytic anemia, thrombocytopenia, mastocytosis, or lymphosarcoma. Apparently, the anti-inflammatory and immunosuppressive effects of cortisol can mask or cause remission of concurrent problems that become clinically obvious after resolution of the hypercortisolemia.

DIABETES MELLITUS

Alterations of glucose metabolism frequently occur in dogs with hyperadrenocorticism. Approximately 40% to 60% of dogs have fasting hyperglycemia, whereas the prevalence of overt diabetes mellitus in dogs with hyperadrenocorticism is about 10%. Insulin resistance, characterized by the presence of endogenous hyperinsulinemia in the face of a normal or high plasma glucose concentration, also is a common feature of hyperadrenocorticism in dogs. Factors that affect glucose metabolism in dogs with glucocorticoid excess include increased hepatic gluconeogenesis and decreased glucose uptake by peripheral tissues from altered insulin receptor binding and impaired intracellular response to insulin.

The diagnosis of diabetes mellitus in a patient with established hyperadrenocorticism is usually straightforward (blood glucose concentration > 250 mg/dL with glucosuria and/or ketonuria). Often the owner notes a sudden increase in thirst, appetite, and urination in a Cushings’s dog that has been reasonably well-controlled.

The diagnosis of hyperadrenocorticism in dogs with overt diabetes mellitus, on the other hand, is difficult on clinical grounds alone because many clinical signs (polyuria, polydipsia, polyphagia, and hepatomegaly) are common to both disorders. In addition, the complete blood cell count (leukocytosis), serum biochemical profile (increases in serum alkaline phosphatase, alanine aminotransferase, and cholesterol), radiographs, and ultrasound results of the two diseases are often similar. Underlying hyperadrenocorticism should be suspected in any diabetic dog that has or develops bilaterally symmetrical hair loss, abdominal

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lent to ravenous appetites, anorexia or poor appetite during treatment with mitotane suggests over dosage. Administration of glucocorticoid (prednisone, 0.2 mg/kg) daily during the loading phase appears to decrease the severity of or prevent adverse effects by mitigating the rapid fall in serum cortisol levels (glucocorticoid withdrawal).
dogs are asymptomatic for lower urinary tract disease despite the presence of cystic calculi or significant bacteriuria, presumably because of the anti-inflammatory effects of cortisol.

Severe, chronic lower urinary tract infection may enhance potential for ascending infections (pyelonephritis) and renal failure. Pyelonephritis should be suspected when a urinary tract infection cannot be cleared with appropriate antibiotic therapy (based on culture and sensitivity results on urine collected by cystocentesis). Persistent polyuria and polydipsia in well-controlled, nondiabetic Cushing's dogs (pre- and post-ACTH cortisols in normal basal cortisol range) also suggests upper urinary tract infection. Pyelonephritis is best diagnosed by contrast dye studies of the kidneys, renal biopsy, or renal ultrasonography. Clinically, pyelonephritis often mimics antibiotic-responsive polyuria and polydipsia.

**ACUTE PANCREATITIS**

Dogs with hyperadrenocorticism are predisposed to acute pancreatitis. A recent study concluded that hyperadrenocorticism, prior gastrointestinal disease, diabetes mellitus, and hypothyroidism as well as certain breeds (Yorkshire Terrier, Miniature Schnauzer, Toy Poodle), obesity, and small body size are risk factors for the development of acute pancreatitis. Other risk factors include hyperlipidemia, pancreatic duct obstruction, and, possibly, the use of high doses of corticosteroids. Because the clinical signs of pancreatitis are similar to adverse effects of mitotane, the diagnosis and treatment of acute pancreatitis is sometimes delayed in Cushing's dogs being treated with this drug. As a general rule, any dog suspected of mitotane overdose that doesn't respond to glucocorticoid supplementation (0.4 mg/kg) within several hours should be evaluated for another illness. The diagnosis of pancreatitis can often be supported by history (recent fatty meal), physical exam (abdominal pain on palpation), laboratory evaluation (elevated white blood cell count, elevated amylase and lipase levels, rising serum alkaline phosphatase, total bilirubin and cholesterol concentrations), radiography (loss of detail in the cranial abdomen), and ultrasonography (finding an edematous pancreas).

With regard to recommendations for dogs with hyperadrenocorticism and a history of pancreatitis, weight control and low-fat diets should be considered. In dogs suspected of having an adrenocortical tumor with concurrent or previous pancreatitis, the use of the high-dose dexamethasone suppression test for diagnostic purposes should probably be avoided. Instead, endogenous ACTH level determination, adrenal ultrasonography, magnetic resonance imaging or computed tomography scanning can be used to confirm the diagnosis of an adrenocortical tumor.
HYPERTENSION

Systemic hypertension, a classic feature of Cushing's syndrome in humans, occurs in over 50% of dogs with untreated hyperadrenocorticism. Possible mechanisms for sustained increases in blood pressure include secretion of renin substrate (the circulating protein upon which renin acts to release angiotensin I), reduction of vasodilator prostaglandins, increased vascular responsiveness to catecholamines and angiotensin II, and secretion of non-zona glomerulosa mineralocorticoids. More recently, hyperaldosteronism, which may contribute to increased sodium and water retention, has also been linked to Cushing's syndrome and hypertension. Plasma aldosterone levels (pre- and post-ACTH administration) were highest in dogs with untreated pituitary-dependent Cushing's disease, moderately elevated in treated but poorly controlled Cushing's dogs, and near normal in dogs with well-controlled Cushing's disease.

Elevations in blood pressure may cause or contribute to blindness (from intraocular hemorrhage and retinal detachment), thromboembolism, intrarenal hypertension and glomerulosclerosis with proteinuria, left ventricular hypertrophy and congestive heart failure, and pulmonary thromboembolism. In most cases, the hypertension resolves after successful management of the hyperadrenocorticism (improvement can take up to 6 months or longer). However, some dogs remain hypertensive despite good control with medical therapy (mitotane). Additional treatment with antihypertensive medications should be considered in Cushing's dogs with (1) severe hypertension (systolic blood pressure > 190 mm Hg and/or diastolic blood pressure > 130 mm Hg), (2) persistent hypertension despite therapy, or (3) concurrent disorders that may be aggravated by sustained high blood pressure, such as retinopathies, compensated mitral or tricuspid insufficiency, congestive heart failure, glomerulopathies, or pulmonary thromboembolism.

GLomerular DISEASE

Glomerulonephritis is also associated with hyperadrenocorticism. Factors that may predispose dogs with hyperadrenocorticism to glomerulonephritis include altered immune complex solubility (relative antigen excess), frequent occurrence of chronic infections, and decreased clearance of immune complexes by the reticuloendothelial system. In one study, the incidence of glomerular lesions consistent with glomerulonephritis at necropsy of confirmed cases of Cushing's disease was 15% (R Justin, S Moroff, and ME Peterson; unpublished observations, 1991). In other studies, the incidence of significant proteinuria (urine protein to creatinine ratio > 1) in dogs without urinary tract infection (inactive urinary sediment and negative urine culture) ranged from 44% to 75%. These studies suggest that although proteinuria is quite common in dogs with hyperadrenocorticism, not all dogs with proteinuria and hyperadrenocorticism have glomerulonephritis. Other causes of proteinuria that may be associated with hypercortisolemia include glomerulosclerosis, increased glomerular pore size, altered permselectivity, and amyloidosis. In general, proteinuria in most dogs with Cushing's disease is usually mild (urine protein to creatinine ratio, 1.0 to 5.0) and tends to improve or resolve after successful treatment of the hyperadrenocorticism.

The clinical significance of glomerular disease and proteinuria in dogs with hyperadrenocorticism is unclear; however, extrarenal manifestations of glomerulonephritis include thromboembolism and hypertension, which are also serious complications of Cushing's syndrome. Therefore, one could make a strong argument for treatment of all dogs with Cushing's disease and proteinuria and/or hypertension, even if the other clinical signs related to hyperadrenocorticism are mild.

PITUITARY MACROTUMORS

The most common causes of PDH are small ACTH-secreting tumors of the pars distalis (microadenomas). Less commonly, PDH results from a large, so-called macrotumor (tumor size > 1 cm in diameter) (see also the article by Dr. Ilke). These tumors may invade or compress adjacent neural structures resulting in clinical signs that often reflect both the endocrine and space-occupying effects of the tumor. In most cases, CNS signs develop weeks to months after the diagnosis and treatment of PDH, although in some cases neurologic signs precede the diagnosis of hyperadrenocorticism. Early CNS signs noted by owners, which are often subtle, include dullness, anorexia, restlessness, loss of interest in household activities, and brief episodes of disorientation. More definitive signs related to the presence of a macrotumor include ataxia, obtundation and stupor, symmetrical tetraparesis, and pacing. Other neurologic signs such as severe behavior changes, head pressing, blindness, seizures, and coma tend to occur with advanced disease.

The only reliable means of establishing an ante mortem diagnosis of pituitary macrotumor is diagnostic imagery (computed tomography or magnetic resonance imaging). Because approximately 15% to 20% of dogs with PDH and visible pituitary tumors (>3 mm) develop neurologic signs within the first year after diagnosis, diagnostic imaging is recommended as a predictor of which dogs are likely to develop problems from an enlarging pituitary tumor and for dogs with PDH that develop CNS signs not attributable to a metabolic cause. Treatment of pituitary tumors may be attempted with radiotherapy (cobalt irradiation), especially if the diagnosis can be made before profound neurologic signs develop. Dogs showing no or mild CNS signs (subtle behavioral abnormalities) tend to have more complete and rapid
remission of neurologic signs. Dogs showing more advanced neurologic signs such as stupor, head pressing, or coma often have minimal or no response to radiotherapy. A study at The Animal Medical Center showed that the median survival time of dogs with pituitary macrotumors and severe neurologic signs was 50 days (range, 1 to 104 days), compared to a median survival time of 852 days (range, 145 to 1179 days) in dogs with minimal or no neurologic signs. Without treatment, most dogs with CNS signs develop progressive neurologic deterioration within weeks to months.

CONGESTIVE HEART FAILURE

Often, dogs with hyperadrenocorticism have compensated tricuspid or mitral valvular insufficiency. Although uncommon, volume overload from cortisol excess and pressure overload from systemic hypertension may cause cardiac decompensation and congestive heart failure. Treatment of hyperadrenocorticism is therefore recommended for dogs with compensated valvular heart disease. In dogs with congestive heart failure, improved response to cardiac drugs is observed with control of the hyperadrenocorticism.

PULMONARY THROMBOEMBOLISM

Pulmonary thromboembolism (PTE) is a potentially serious and often deadly complication of hyperadrenocorticism. Dogs with untreated hyperadrenocorticism have increased plasma concentrations of vitamin K-dependent factors (II, VII, IX, X) and platelet-derived factors V and vWF:Ag compared to normal dogs. Increased hepatic synthesis of vitamin K-dependent coagulation factors and platelet synthesis or release of factors V and vWF:Ag plays a major role in causing hypercoagulability in dogs with Cushing's syndrome. Other conditions or disorders that predispose to thrombosis in humans and that are common to dogs with hyperadrenocorticism include increased hematocrit (vascular stasis), obesity, hypertension, acute pancreatitis, protein-losing nephropathies, and diabetes mellitus.

No clinical signs are pathognomonic for PTE, although affected dogs usually develop an acute onset of respiratory distress (tachypnea, cyanosis, dyspnea). Thoracic radiographs may be normal in dogs with PTE. Usually, however, radiographic changes include pleural effusion, pulmonary infiltrates, increased diameter and blunting of pulmonary arteries, decreased vascularity of affected lung lobes, and increased vascularity of lobes without thrombosis. Arterial blood gas determinations usually reveal a decrease in $P_{O_2}$ below 70 mm Hg (normal 80 to 100 mm Hg) and a decrease in $P_{CO_2}$ in the range of 12 to 30 mm Hg (normal 35 to 45 mm Hg). Thrombosis may be confirmed with pulmonary angiography or a radionuclear lung scan.

Because no pathognomonic signs exist for PTE and definitive diagnostic tests are either invasive (pulmonary angiography) or not widely available (radionuclear scans) and, if performed, may actually jeopardize the life of the patient (removing dyspneic and cyanotic patients from oxygen support to perform diagnostic procedures is unwise), the diagnosis of PTE is often made based on clinical impression. Dogs that have risk factors for PTE, a history of acute nonspecific cardiopulmonary signs, and supportive radiographs (although radiographs may reveal no abnormalities) and blood gas analysis have PTE until proven otherwise and should be treated aggressively.

Treatment of PTE in dogs with hyperadrenocorticism is based on clinical experience and extrapolation from human studies and includes cage rest, provision of oxygen and anticoagulants, and general supportive care. Heparin is considered the mainstay of therapy for PTE. It is effective in preventing reemobilization while allowing fibrinolysis to proceed. Treatment begins with an intravenous bolus of heparin (100 to 200 U/kg), usually followed by maintenance heparin (250 U/kg SC every 6 to 8 hours). Maintenance heparin should be titrated to achieve an activated partial thromboplastin time (APTT) or activated clotting time (ACT) of at least 1.5 times the control values. The use of plasma to replenish antithrombin III is probably not necessary because recent studies suggest that the hypercoagulable state associated with hyperadrenocorticism is not related to antithrombin III deficiency. Recently, the thrombolytic agent streptokinase was used successfully in four dogs with PTE, with minimal side effects. Because of extreme expense and the increased risk of bleeding associated with thrombolytic agents (streptokinase and recombinant tissue plasminogen activator), thrombolytic therapy is usually reserved for massive PTE with cardiovascular compromise.

Because the prognosis for PTE is guarded to grave, prophylactic low-dose heparin may be appropriate in dogs with Cushing's disease that have increased risk of thrombosis. Low-dose heparin administration has been documented to provide efficacious and safe prophylaxis in human patients with low to moderate risk of deep vein thrombosis. This situation in dogs would include surgical patients with adrenocortical tumors who are scheduled for adrenalectomy, because surgery and neoplasia are additional risk factors for PTE. The low-dose heparin regimen for dogs is 70 U/kg SC every 8 to 12 hours, starting before the surgical procedure and continuing until the day of hospital dismissal. Monitoring anticoagulation effects is not necessary because the low dose of heparin usually does not alter the APTT or ACT. Limited clinical experience in dogs suggests that low-dose heparin administration is safe; however, efficacy studies have not been performed.
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ADRENAL DISORDERS IN CATS

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Adrenal diseases are uncommon endocrine disorders in cats. Of those adrenal diseases recognized in the cat, hyperadrenocorticism has been reported most frequently, followed by hypoadrenocorticism. Pheochromocytomas and aldosterone-secreting tumors have been reported rarely. In this article, we summarize information from previously reported cases of feline adrenal disease and from unreported cases we have observed.

HYPERADRENOCORTICISM

Etiology

Hyperadrenocorticism results from the excessive production of glucocorticoids. As in the dog, hyperadrenocorticism in the cat can arise from disease of the pituitary or adrenal gland. Pituitary-dependent hyperadrenocorticism results from excessive secretion of adrenocorticotrophic hormone (ACTH) from the pars distalis or pars intermedia of the pituitary gland, which in turn induces bilateral adrenocortical hyperplasia and hypercortisolism. Excess secretion of ACTH may arise from neoplastic or, less commonly, hyperplastic pituitary corticotroph cells. Of 57 reported cases73, 14, 19, 22-24, 28, 32, 39, 45, 47, 49, 63, 66, 80-82, 86 and two observed cases (CA Duesberg, unpublished observations, 1994 and 1996) of hyperadrenocorticism in the cat, 48 cats (81%) have had pituitary-dependent disease and 11 cats (19%) have had an adrenocortical tumor. Adrenocortical tumors secrete excessive cortisol autonomously, escaping the nor-

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