VETERINARY EMERGENCY CLINIC

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# AN UPDATE ON ATYPICAL HYPERADRENOCORTICISM

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Atypical hyperadrenocorticism is defined as a syndrome in which a dog appears to have hyperadrenocorticism based on history, physical examination and clinicopathologic findings but a low dose dexamethasone suppression test, urine cortisol creatinine ratio test and ACTH stimulation tests fall into the currently accepted reference range. This is an uncommon endocrine disorder, which affects middle aged to older dogs and clinically may mimic the signs of hyperadrenocorticism. This disease is thought to be a result of overproduction of estradiol, androstenedione, progesterone, and 17-hydroxyprogesterone in addition to cortisol. The disease process may be a result of adrenal hyperplasia, adrenal tumours or a functional pituitary microadenoma. It is more common to have the adrenal form of the disease; however both forms have been documented.

Clinical signs may be include polyuria, polydipsia, polyphagia, lethargy, abdominal distension, muscle weakness, or recurrent urinary tract infections. Dogs may also present with dermatological signs as their primary complaint. These dermatological abnormalities may include truncal alopecia, thin skin, comedones, bruising, cutaneous hyperpigmentation, calcinosis cutis, pyoderma, dermal atrophy, secondary demodicosis and seborrhea. Abnormalities to a dogs reproductive status may also be noted and include perianal adenoma in females or castrated males, clitoral hypertrophy in female dogs, behavioural estrus in spayed females, testicular atrophy in intact males, prostomegaly in castrated males or behavioural or physical signs of testosterone excess.

Common laboratory abnormalities include an elevated alkaline phosphatise, an elevated ALT, hypercholesterolemia, hyperglycemia, and a decreased BUN. Sterile urinary tract infections (urinary tract infections without pyuria and bacteriuria) and proteinuria may be noted on a urinalysis. Lastly sick euthyroid syndrome may be noted.

The diagnostic approach for this syndrome involves ensuring that there is a strong suspicion of hyperadrenocorticism based on appropriate clinical signs and laboratory abnormalities. A low dose dexamethasone suppression test should be performed, which will not support a diagnosis of hyperadrenocorticism. Similarly if performed an ACTH stimulation test and a urine cortisol creatinine ratio test will not support a diagnosis of hyperadrenocorticism. Abdominal ultrasound is recommended as part of this diagnostic work up. Generally speaking this form of hyperadrenocorticism tends to be caused by an adrenal tumour. If no tumour is visualized using ultrasonography or using advanced imaging; it does not rule out the presence of the disease as secretion of sex hormones and intermediate adrenal hormones may suppress pituitary ACTH secretion and cause atrophy of normal adrenocortical tissue. Currently the most sensitive and specific test for atypical hyperadrenocorticism is the University of Tennessee Veterinary Endocrinology laboratory's adrenal androgen panel. This test is performed using the same method as a traditional ACTH stimulation test; and evaluates baseline and post stimulation cortisol, progesterone, 17-hydroxyprogesterone, estradiol, androstenedione and aldosterone levels.

Multiple treatment modalities are recommended for this disease process. Treatment is influenced by which intermediate adrenal hormones are elevated on the individual adrenal androgen panel. Melatonin can be used as it has anti-gonadotropic activity and will inhibit aromatase enzymes in tissue, which decreases androstenedione and testosterone conversion into estradiol. It also inhibits the 21-hydroxylase enzyme, which lowers cortisol levels. It is important to treat for at least 4 months for this treatment to be effective. Lignans can be used as they have phytoestrogenic activity and will compete with estradiol for tissue estrogen receptors with less biological effect. They will also inhibit aromatase enzyme, which lowers estradiol and inhibits the 3-beta hydroxysteroid dehydrogenase enzyme, which lowers cortisol. Lysodren therapy is very effective at suppressing cortisol, progesterone, androstenedione and 17-hydroxyprogesterone levels. Estradiol is not always suppressed by Lysodren therapy. Some research demonstrates that this is the preferential therapy for atypical hyperadrenocorticism. Trilostane therapy has been used, however has been found to be ineffective in many cases as it increases 17-hydroxyprogesterone serum levels and has also been found to intermittently increase estradiol and androstenedione as well. Ketoconazole is thought to be a good therapy in cases with both increased estradiol concentrations and elevated intermediate adrenal steroid levels. The mechanism of action is inhibition of 17-hydroxyprogesterone early in the adrenal pathway and inhibition of 11-beta hydroxylase enzyme later in the pathway.

In summary atypical hyperadrenocorticism is an uncommon endocrine disorder of dogs with clinical signs, which are suggestive of hyperadrenocorticism; however traditional ACTH stimulation test, low dose dexamethasone suppression test, and urine cortisol creatinine ratio will not yield a positive diagnosis. The specificity for adrenal panels is low, therefore it is only recommended to test for atypical HAC when moderate to severe clinical signs are present.