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Diagnosis of Hyperadrenocorticism in Dogs

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A presumptive diagnosis of hyperadrenocorticism in dogs can be made from clinical signs, physical examination, routine laboratory tests, and diagnostic imaging findings, but the diagnosis must be confirmed by use of pituitary-adrenal function tests. Screening tests designed to diagnose hyperadrenocorticism include the corticotropin (adrenocorticotropic hormone; ACTH) stimulation test, low-dose dexamethasone suppression test, and the urinary cortisol:creatinine ratio. None of these screening tests are perfect, and all are capable of giving false-negative and false-positive test results. Because of the limitation of these diagnostic tests, screening for hyperadrenocorticism must be reserved for dogs in which the disease is strongly suspected on the basis of historical and clinical findings. Once a diagnosis has been confirmed, the next step in the workup is to use one or more tests and procedures to distinguish pituitary-dependent from adrenal-dependent hyperadrenocorticism. Endocrine tests in this category include the high-dose dexamethasone suppression test and endogenous plasma ACTH measurements. Imaging techniques such as abdominal radiography, ultrasonography, computed tomography, and magnetic resonance imaging can also be extremely helpful in determining the cause.
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Hyperadrenocorticism (Cushing's syndrome) is a constellation of clinical findings and biochemical abnormalities caused by chronic overproduction of cortisol by the adrenal cortices.[1-4] The purpose of this review is to discuss the available diagnostic tests used to distinguish normal dogs from those with hyperadrenocorticism and, once a diagnosis of hyperadrenocorticism has been confirmed, to discuss the tests and procedures available to help distinguish pituitary-dependent hyperadrenocorticism from cortisol-secreting adrenocortical neoplasia.

Unfortunately, none of the diagnostic tests used in dogs with suspected hyperadrenocorticism are totally reliable, and both false-positive and false-negative results are common. Because there are inherent problems with these diagnostic tests, the veterinarian is frequently challenged when attempting to properly interpret the dog's tests results. It is important to remember, however, that the predictive value of a positive screening test result for hyperadrenocorticism increases in direct proportion to the number and severity of clinical signs and biochemical changes that develop in this disease.[2-5] Therefore, one must always remember the importance of the dog's signalment, history, and physical examination findings when interpreting the diagnostic test results of all pituitary-adrenal function tests.

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Causes of Hyperadrenocorticism

There are three major causes of hyperadrenocorticism in dogs. The syndrome can be caused by oversecretion of corticotropin (adrenocorticotropic hormone; ACTH) by the pituitary gland (pituitary-dependent hyperadrenocorticism), cortisol-secreting adrenocortical neoplasia (adrenal-dependent hyperadrenocorticism), or iatrogenic administration of glucocorticoids.[1-4]

Pituitary-Dependent Hyperadrenocorticism

Pituitary-dependent hyperadrenocorticism is the most common cause of naturally occurring hyperadrenocorticism in dogs, accounting for 80 to 85% of cases.[1-4] The excessive secretion of ACTH from pituitary microadenoma, macroadenoma, corticotroph hyperplasia, or (very rarely) adenocarcinoma results in bilateral adrenocortical hyperplasia.[6,7]

Most dogs with pituitary-dependent hyperadrenocorticism have a pituitary tumor, with adenomas of the corticotropic cells of the pars distalis and pars intermedia being the most common tumor type.[6,7] Although the reported incidence of corticotropic adenomas associated with pituitary-dependent hyperadrenocorticism varies, this is probably

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more to do with the fact that detection of small tumors requires careful microdissection, experience, and special stains. In one study using immunocytochemical staining, more than 80% of dogs with pituitary-dependent hyperadrenocorticism were positive for pituitary adenomas.[7]

Most pituitary tumors in dogs with pituitary-dependent hyperadrenocorticism are microadenomas, defined as a tumor less than 10 mm diameter. Only about 10 to 15% of dogs have large corticotropic adenomas (macroadenomas) at the time of diagnosis.[7,8] These may compress the remaining pituitary gland and extend dorsally into the hypothalamus. However, they are generally slow growing and may not produce neurological signs. Although reported, corticotropic adenocarcinomas are rare.[6]

Adrenal-Dependent Hyperadrenocorticism

Cortisol-secreting adrenocortical tumors are responsible for approximately 15 to 20% of dogs with naturally occurring Cushing's syndrome.[1-4] The vast majority of adrenocortical tumors in these dogs are unilateral, but bilateral adrenal tumors do occur.[9]

Adrenocortical tumors may be benign or malignant, although it can be difficult histologically to distinguish between an adrenocortical adenoma and a carcinoma unless there is evidence of invasion or metastasis.[3] In dogs, adrenocortical adenomas and carcinomas occur with approximately equal frequency.[1-4] Adrenocortical adenomas are usually small, well-circumscribed tumors that do not metastasize and are not locally invasive. In contrast, adrenocortical carcinomas are usually large, locally invasive, hemorrhagic, and necrotic. Tumor calcification also occurs in over 50% of dogs with adrenal carcinoma.[10,11] Carcinomas, especially of the right adrenal, frequently invade the phrenicoabdominal vein and caudal vena cava and metastasize to the liver, lung, and kidney.[2]

Dogs with adrenocortical adenomas or carcinomas secrete cortisol autonomously, or independent of pituitary ACTH control. Through the negative-feedback effects of glucocorticoids on the pituitary gland, the excess cortisol secreted by the adrenal tumor chronically suppress endogenous ACTH secretion, resulting in atrophy of the contralateral ("normal") adrenal cortex.[2,3] This fact becomes extremely important to remember if the tumor is to be removed surgically, inasmuch as the dog will almost invariably develop hypoadrenocorticism postoperatively and will require temporary glucocorticoid supplementation. Because ACTH is not the primary stimulus for aldosterone secretion from the adrenal, however, the function of the zona glomerulosa will not be affected and mineralocorticoid supplementation will not be required.[2,3]

Iatrogenic Hyperadrenocorticism

Iatrogenic hyperadrenocorticism results in clinical signs and physical examination findings similar to those seen in the natural disease. Excessive or prolonged administration of corticosteroids causes iatrogenic hyperadrenocorticism. Because of the negative-feedback effects of glucocorticoids on the pituitary gland, endogenous ACTH production is suppressed, resulting in atrophy of the adrenal cortices.

Other Potential Causes of Hyperadrenocorticism

There are also a few reports of dogs with pituitary-dependent hyperadrenocorticism having concurrent adrenal tumors.[12] Bilateral cortisol-secreting adrenal tumors have also been reported but appear to be extremely rare.[9]

In the ectopic ACTH syndrome, nonpituitary tumors synthesize and secrete ACTH, which, in turn, ultimately cause bilateral adrenocortical hyperplasia and hypercortisolism. Ectopic ACTH production is not commonly recognized in the dog, but in humans a number of tumors (eg, oat cell carcinomas of the lung, pancreatic islet cell tumors, and carcinoid tumors) are capable of synthesizing and secreting excessive quantities of ACTH. Recently, ectopic ACTH secretion was described in two dogs with hyperadrenocorticism and abdominal neuroendocrine tumors.[13,14]

Signalment

Age, Breed, and Sex

Pituitary-dependent hyperadrenocorticism is usually a disease of the middle-aged to older dogs, with a median age of approximately 10 to 11 years.[1-4] Dogs with adrenal-dependent hyperadrenocorticism tend to be slightly older, with a median age of 11 to 12 years.[3,11]

Any breed can develop hyperadrenocorticism but poodles, dachshunds, and small terriers, for example, the Yorkshire terrier, Jack Russell terrier, and Staffordshire bull terrier, appear more at risk at developing pituitary-dependent hyperadrenocorticism. Adrenocortical tumors occur more frequently in larger breeds with about 50% of dogs weighing greater than 20 kg.[3,11]

There is no appreciable difference in sex distribution in pituitary-dependent hyperadrenocorticism; however, female dogs are more likely to develop adrenal tumors than males. In one survey, between 60 and 65% of dogs with functional adrenocortical tumors were female.[3,11]

History, Clinical Signs, and Physical Examination

Hyperadrenocorticism has an insidious onset and is slowly progressive over many months or even years. Many owners consider the early signs as part of the normal aging process of their dog. In a few cases, clinical signs may be intermittent, with periods of remission and relapse, whereas in others there may be an apparent rapid onset and progression of clinical signs. Larger breeds of dogs and those with recent onset of disease, however, may only show a few characteristic signs rather than the classic array of clinical signs usually observed in smaller breeds. Recent corticosteroid administration (including eye, ear, and topical preparations) should be ascertained, to exclude iatrogenic hyperadrenocorticism.

The most common clinical signs associated with hyperadrenocorticism in dogs are polydipsia, polyuria, polyphagia, lethargy, abdominal enlargement or potbelly, panting, obesity, muscle weakness, and recurrent urinary tract infections. Dermatologic manifestations of hyperadrenocorticism commonly include truncal hair thinning or alopecia.[1-4] On phys-