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# DIAGNOSIS OF CUSHING'S SYNDROME: SO MANY WAYS TO ONE DESTINATION

Spontaneous hypercortisolism or Cushing's syndrome is characterized by physical and biochemical changes resulting from chronic exposure to elevated concentrations of circulating glucocorticoid. About 80-85% of cases of hypercortisolism in dogs are adrenocorticotropin (ACTH)-dependent, most often the result of excessive secretion of ACTH by a pituitary corticotroph adenoma. In the remaining cases hypercortisolism is ACTH-independent, the result of excessive secretion of glucocorticoids by an adrenocortical tumor (AT). The ectopic ACTH secretion syndrome and ACTH-independent or primary bilateral adrenal hyperplasia are both rare in dogs [1].

The pituitary lesions producing excess ACTH range from small nests of hyperplastic corticotrophs (or melanotrophs) to micro- or macroadenomas. Pituitary macroadenomas can eventually invade surrounding tissues such as the cavernous sinus, dura mater, brain, and rarely the sphenoid bone. These are called invasive adenomas, to distinguish them from pituitary tumors with extracranial metastasis, which are a rare in dogs.

Cortisol-secreting ATs can be divided into adenomas and carcinomas, but histological differentiation is not always straightforward. Histological markers of adrenocortical carcinoma include vascular invasion, intracapsular growth, and atypical nuclei [2]. However, the most reliable indicator of malignancy at present is metastasis.

**Establishing the diagnosis of hypercortisolism**

Cushing's syndrome is a disease of middle-aged and older dogs. There is no gender predilection. It occurs in all breeds, with a slight predilection for small breeds such as the dachshund and the miniature poodle. Many of the clinical signs can be related to the biochemical effects of glucocorticoids, namely, gluconeogenesis and lipogenesis at the expense of protein. In dogs, the cardinal physical features are centripetal obesity, alopecia, and atrophy of muscles and skin. Abdominal palpation may reveal hepatomegaly [1]. Polyuria and polyphagia are also prominent features. The polyuria is known to be due to impaired osmoregulation of vasopressin release and interference by the glucocorticoid excess with the action of vasopressin in the kidney.

The biochemical diagnosis of hypercortisolism depends on the demonstration of two characteristics: increased production of cortisol and decreased sensitivity to glucocorticoid feedback. The diagnostic approach has been reviewed recently in a consensus statement by leading veterinary endocrinologists [3]. It has been agreed that in dogs with clinical signs of hypercortisolism, the diagnosis should be confirmed by tests of cortisol secretion and the integrity of the feedback system. The low-dose dexamethasone suppression test (LDDST) is the most recommended test for this purpose. Measurement of plasma cortisol at 4 and 8 hours after dexamethasone administration is recommended to differentiate between pituitary- and adrenal-dependent hypercortisolism. Measurement of the urinary corticoid to creatinine ratio is a convenient test for hypercortisolism, if performed at home to avoid the influence of stress [9]. Urinary corticoid excretion represents an integrated measure of corticoid production over an interval (usually one night), smoothing the effects of short-term fluctuations in plasma cortisol concentration. As it can be easily combined with the HDDST, the two forms of hypercortisolism can be differentiated in one test, but its reliability depends on the availability of the a trustworthy assay. The ACTH stimulation test, which has been used in the diagnosis of spontaneous hypercortisolism in dogs for quite some time, is no longer recommended [3]. In principle it is a test of adrenocortical reserve capacity, used to diagnose primary and secondary adrenocortical insufficiency. It can thus be used to diagnose iatrogenic hypercortisolism, which via feedback suppression results in secondary adrenocortical insufficiency. In addition, this test is now often used to monitor treatment with trilostane. Measurement of plasma ACTH concentration is useful to differentiate between the adrenal- and pituitary-dependent forms of hypercortisolism, but not for other diagnostic purposes [1]. Plasma ACTH concentration is expected to be low or undetectable in adrenal hypercortisolism but in cases of pituitary tumor it may be elevated or within the normal range, because of the pulsatile secretion pattern of ACTH.

**Diagnostic imaging of the pituitary and adrenal glands**

Diagnostic imaging of the pituitary and adrenals is of great value in determining the best treatment and for objectively evaluating the prognosis. The pituitary can be visualized by computed tomography (CT) or nuclear magnetic resonance imaging (MRI) [4]. In healthy dogs, the pituitary gland is 6 to 10 mm in length, 5 to/9 mm in width, and 4 to/6 mm in height. The size of the pituitary can be evaluated by means of the ratio between its height and the area of the brain (P/B ratio), measured on a CT image through the center of the pituitary: a P/B ratio greater than 0.31 indicates pituitary enlargement [5].

Macroadenomas of the pituitary are easily detected on contrast-enhanced CT images because they alter the size and shape of the gland, but a normal appearance does not exclude the possible presence of a microadenoma. The classification of pituitary adenomas in humans as microadenomas (0.10 mm) and macroadenomas (10 mm) is not useful in dogs, where adenomas between 6 and 10 mm in height enlarge the gland and therefore cannot be classified as microadenomas. Direct visualization of the pituitary adenoma is only possible when the imaging characteristics of the adenoma are different from those of the surrounding normal pituitary tissue. The enhancement pattern of the neurohypophysis during dynamic contrast enhanced CT has been called the 'pituitary flush'. The displacement, distortion, or disappearance of the pituitary 'flush sign' in the early phase of dynamic CT examinations can be used to identify both micro- and macroadenomas in dogs.

The adrenal glands can also be visualized by CT [6], but ultrasonography is less expensive, requires less time, and does not require anesthesia, and so it is often used first [7]. Attention has been given to the symmetry, size, shape, and echogenicity of adrenal glands. Bilateral enlargement of the adrenal glands is expected in PDH, while a cortisol-secreting AT usually presents as a unilateral adrenal mass with atrophy of the contralateral adrenal. Determining the size of the adrenals has been controversial. An adrenal diameter greater than 7 mm has been reported to signify hyperplasia, with a sensitivity of 77% and specificity of 80%. Recently, Choi and coauthors [8] reported that in dogs weighing less than 10 kg a diameter greater than 6 mm indicates PDH, with a sensitivity of 75% and a specificity 94%. The structure of the adrenal may be more important than its size. In hyperplastic adrenal glands the normal shape is preserved and the sonographic appearance is homogeneous. Contrast-enhanced ultrasonography is a relatively new approach in evaluating adrenal glands [8]. During this procedure, the contrast agent is administered IV and time-intensity curves are generated for the adrenal cortex, adrenal medulla, and ipsilateral renal artery of both adrenal glands. Contrast-enhanced ultrasonography is able to detect vascular changes induced by hypercortisolism. In normal dogs, contrast enhancement distribution in the adrenals is homogeneous and in the washout phase there is a gradual and homogeneous decrease in enhancement. In dogs with PDH, there is rapid, chaotic, and simultaneous contrast enhancement in both the cortex and the medulla. In addition, the peak contrast intensity in both the cortex and the medulla was twice as high in dogs with PDH compared with that of healthy controls [9]. Further studies are needed to determine whether reference ranges for clinically normal dogs and dogs with PDH can be determined and applied in clinical settings. This approach may be promising in the diagnosis of bilateral adrenocortical tumor as well as in differentiating between tumor and adrenocortical hyperplasia. Especially differentiation between bilateral cortisol-secreting ATs and hyperplastic adrenals is challenging. Bilateral ATs are not very common and it is a heterogeneous echographic appearance, reflecting necrosis and hemorrhage in the adrenals, which may suggest tumor rather than hyperplasia. Asymmetry of the adrenal glands is a typical ultrasonographic finding with a unilateral cortisol-secreting AT. In addition to the size and structure of an AT, its expansion into blood vessels and possible metastasis to the liver are also evaluated. If nodular structures are revealed in the liver, ultrasound-guided needle aspiration biopsy can be performed. Radiographs or a CT scan of the thorax should be made to determine whether there are metastases in the lungs.

**References**

1. Galac S, Reusch C, Kooistra H, Rijnberk A. Adrenals. In: Clinical Endocrinology of Dogs and Cats. Hannover, Germany: Schlutersche; 2010, 93-154.
2. Labelle P, Kyles E, Farver TB, de Cock HEV. Indicators of malignancy of canine adrenocortical tumors: Histopathology and proliferation index. Vet Pathol 2004,41:490-497.
3. Behrend EN, Kooistra HS, Nelson R, Reusch CE, Scott-Moncrieff JC. Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (small animal]. J Vet Intern Med 2013,27:1292-1304.

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4. Auriemma E, Barthez PY, van der Vlugt-Meijer RH, Voorhout G, Meij BP. Computed tomography and low-field magnetic resonance imaging of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism: 11 cases (2001-2003). J Am Vet Med Assoc 2009, 15:409-414.
5. Kooistra HS, Voorhout G, Mol JA, Rijnberk A. Correlation between impairment of glucocorticoid feedback and the size of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. J Endocrinol 1997,152:387-394.
6. Rodriguez Pineiro MI, de Fornel-Thibaud P, Benchekroun G, Garnier F, Maurey-Guenec C, Delisle F, et al. Use of computed tomography adrenal gland measurement for differentiating ACTH dependence from ACTH independence in 64 dogs with hyperadenocorticism. J Vet Intern Med 2011,25:1066-1074.
7. Barthez PY, Nyland TG, Feldman EC. Ultrasonographic evaluation of the adrenal glands in dogs. J Am Vet Med Assoc 1995,1:1180-1183.
8. Choi J, Kim H, Yoon J. Ultrasonographic adrenal gland measurements in clinically normal small breed dogs and comparison with pituitary-dependent hyperadrenocorticism. J Vet Med Sci. 2011,73:985-959.
9. Pey P, Vignoli M, Haers H, Duchateau L, Rossi F, Saunders JH. Contrast-enhanced ultrasonography of the normal canine adrenal gland. Vet Radiol Ultrasound. 2011,52:560-567.