Concurrent pituitary and adrenocortical lesions on computed tomography imaging in dogs with spontaneous hypercortisolism

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Background: Spontaneous hypercortisolism or Cushing's syndrome in dogs is either pituitary or adrenal dependent, but concurrent pituitary and adrenal hypercortisolism also has been reported.

Objective: To determine how often concurrent pituitary and adrenal lesions are present in dogs with spontaneous hypercortisolism.

Animals: Two hundred one client-owned dogs with spontaneous hypercortisolism.

Methods: Retrospective study. Pre- and post-contrast computed tomography (CT) scans of the pituitary and adrenal glands were performed in dogs with confirmed hypercortisolism.

Results: In dogs with dexamethasone-suppressible hypercortisolism (122/201), 78 dogs (64%) had an enlarged pituitary gland (median pituitary height/brain area [P/B], 0.43 × 10⁻² mm⁻¹; range, 0.32-1.21 × 10⁻² mm⁻¹). Two of these 78 dogs had concurrent adrenal lesions. In the remaining dogs (44/122; 36%), the pituitary gland was not enlarged. In the dexamethasone-resistant group (79/201), the pituitary gland was enlarged in 47 dogs (59%; median P/B, 0.57 × 10⁻²; range, 0.32-1.50 × 10⁻² mm⁻¹). Eight of these 47 dogs (17%) had concurrent adrenal lesions. In the remaining 32 dexamethasone-resistant dogs (41%), the pituitary gland was not enlarged. Among them, 27 dogs had adrenal lesions and suppressed ACTH concentrations consistent with adrenal-dependent hypercortisolism and 5 dogs were diagnosed with pituitary-dependent hypercortisolism.

Conclusions and Clinical Importance: Concurrent pituitary and adrenal lesions were present in 5% of all dogs with hypercortisolism and in 10% of the dexamethasone-resistant dogs. Diagnostic imaging of both pituitary and adrenal glands should be included in the diagnostic evaluation of every dog with spontaneous hypercortisolism to obtain information needed for estimation of prognosis and choosing the optimal treatment.

KEYWORDS
ACTH, CT scan, Cushing's, diagnostic imaging

INTRODUCTION

Spontaneous hypercortisolism or Cushing's syndrome is 1 of the most common endocrine disorders in dogs. The biochemical diagnosis depends on the demonstration of increased cortisol production or decreased sensitivity to glucocorticoid feedback. The endocrine tests of choice are the low-dose dexamethasone suppression test (LDDST) and determination of the urinary corticoid-to-creatinine ratio (UCCR), preferentially combined with a high-dose dexamethasone suppression test (HDDST). In approximately 80%-85% of affected dogs, spontaneous hypercortisolism is pituitary-dependent hypercortisolism (PDH). In these dogs, a corticotroph adenoma secretes inappropriate and unregulated amounts of ACTH. The remaining 15% of cases of

Abbreviations: ADH, adrenal-dependent hypercortisolism; AT, adrenocortical tumor; HDDST, high-dose dexamethasone suppression test; LDDST, low-dose dexamethasone suppression test; P/B value, pituitary height/brain area value; PDH, pituitary-dependent hypercortisolism; PT, pituitary tumor; UCCR, urinary corticoid to creatinine ratio.
spontaneous hypercortisolism are adrenal-dependent hypercortisolism (ADH). The ACTH-independent hypersecretion of cortisol in these dogs is caused by an adrenocortical adenoma or carcinoma.1,3

Differentiating between PDH and ADH is important, because the optimal treatment may be quite different. Pituitary-dependent hypercortisolism can be managed medically (ie, with trilostane or mitotane), but this approach does not limit growth of the pituitary tumor (PT).3 Hypophysectomy is therefore the treatment of choice, especially in relatively young dogs with an enlarged pituitary gland that may lead to compression of the brain.6,5 Alternatively, radiotherapy can be used.6,7 In dogs with ADH, adrenalectomy is the best treatment option, particularly because of potential malignancy.8–10

To differentiate between PDH and ADH, suppression tests (ie, LDDST or HDDST), measurement of plasma ACTH concentration and diagnostic imaging can be used.7,11,12 A decrease of ≥50% in plasma cortisol concentration or UCCR after administration of dexamethasone implies dexamethasone-suppressible hypercortisolism, which is consistent with PDH.2,13 In dogs with PDH, inappropriate and unregulated secretion of ACTH causes intermittent increase in plasma ACTH concentration, whereas in dogs with ADH, plasma ACTH concentration is suppressed because of negative feedback of cortisol at the hypothalamic-pituitary axis. Computed tomography or MRI can be used to visualize both the pituitary and adrenal glands.3 However, in most dogs with hypercortisolism, only abdominal ultrasonography is used as diagnostic imaging technique, mainly because it is easily accessible, relatively inexpensive, and can be performed without anesthesia.14–17 This approach may result in missing essential information required for an adequate therapeutic plan. If ultrasonography identifies bilateral adrenal enlargement, suggesting PDH, the size of the pituitary gland remains unknown. In case of an adrenocortical tumor (AT), imaging of the thorax is important to search for metastases and CT imaging is the method of choice. Moreover, concurrent endocrine neoplasms have been described, and dogs with spontaneous hypercortisolism caused by an AT also may have a PT.18–20 If both pituitary and adrenal lesions are present, abdominal ultrasonography leads to an incomplete diagnosis if pituitary size and ACTH secretion are not measured. This scenario emphasizes the importance of considering concurrent PT and AT in dogs with hypercortisolism. The objective of our retrospective study was therefore to analyze how often concurrent pituitary and adrenal lesions are present in dogs with hypercortisolism. For this purpose, the endocrine and CT imaging data of a large number of dogs diagnosed with hypercortisolism were evaluated.

2 | MATERIALS AND METHODS

2.1 | Animals and tests

For this retrospective study, the clinical records of dogs diagnosed with hypercortisolism, referred to the Department of Clinical Sciences of Companion Animals and Division of Diagnostic Imaging, Faculty of Veterinary Medicine, Utrecht University, the Netherlands, over a 10-year period (2005–2015) were reviewed. All dogs included had history, physical examination, and biochemical and hematological findings consistent with hypercortisolism.

In all dogs included in the study, the diagnosis of hypercortisolism was confirmed by an endocrine function test, that is, LDDST or UCCR combined with PO HDDST. Both tests were performed and interpreted as described previously.2,21 Blood samples for cortisol (LDDST) and ACTH measurements were collected from the jugular vein and transferred to heparin-coated tubes and ice-chilled EDTA-coated tubes, respectively. Urine samples for UCCR determination were collected by the owner at home, at least 2 days after a veterinary consultation or other potentially stressful event.12 The plasma cortisol concentrations, plasma ACTH concentrations, and UCCRs were determined as described previously.13,22,23 In the LDDST, cortisol concentrations >40 nmol/L at 8 hours post-dexamethasone administration were considered consistent with hypercortisolism. Dogs in which the plasma cortisol concentration in the 4 hours, 8 hours, or both samples was <50% compared to the basal plasma cortisol concentration (0 hours) were designated as dexamethasone-suppressible. A mean UCCR of >10 × 10−6 of 2 urine samples collected on consecutive days was considered consistent with hypercortisolism. Dexamethasone-suppressible hypercortisolism indicating PDH was diagnosed when the UCCR of the third urine sample was <50% of the basal UCCR. Dogs in which the plasma cortisol concentration or UCCR was ≥50% after dexamethasone administration were diagnosed with dexamethasone-resistant hypercortisolism. In these dogs, further discrimination between PDH and ADH was done by measuring basal plasma ACTH concentration. An ACTH concentration of >40 ng/L was interpreted as nonsuppressed and considered compatible with PDH.13

2.2 | Computed tomography

Diagnostic imaging of the pituitary and adrenal glands was performed in all dogs in the study. At our referral center, CT imaging is a first-line procedure in dogs diagnosed with hypercortisolism. The CT imaging was performed under general anesthesia with a single slice helical CT scanner (Secura CT Scanner; Phillips, Best, The Netherlands), using a protocol described previously.24,25 Native-phase CT scans were followed by dynamic CT imaging through the pituitary fossa to analyze the contrast enhancement pattern of the neurohypophysis, called the pituitary flush. Displacement, distortion, or disappearance of the pituitary flush in nonenlarged pituitary glands was interpreted as consistent with the presence of a pituitary microadenoma. On the post-contrast CT image with the largest pituitary height, the pituitary height/brain area (P/B) was calculated to allow correction for the size of the dog and to distinguish nonenlarged (P/B ≤ 0.31 × 10−2 mm−1) from enlarged (P/B > 0.31 × 10−2 mm−1) pituitary glands,26,27

Subsequently, post-contrast CT scanning from the liver to the caudal aspect of the left kidney was performed. On cross-sectional images, the structure, shape, and symmetry of both adrenal glands were evaluated.27–29 The dorsovenous thickness of the cranial and caudal poles of both adrenal glands was measured, and invasion into blood vessels was determined. The adrenal gland was considered enlarged if the maximum thickness was >7 mm.29,30 Bilateral normalized or symmetrically enlarged adrenal glands with a normal peanut-shape and contrast uptake, normal corticomedullary distinction, and no invasion into blood vessels were considered consistent with adrenocortical hyperplasia secondary to PDH. Abnormal adrenal gland...
shape with heterogeneous contrast uptake in combination with increased adrenal thickness (>7 mm), invasion into blood vessels, or both were considered consistent with an adrenal lesion suggestive of AT.31–33 In these cases, CT scanning was expanded to the thorax to search for visible metastases.

2.3 | Histopathology

Histopathological evaluation of the pituitary and adrenal gland tumors was performed as described previously.34,35

2.4 | Data analysis

Descriptive statistical analysis was performed using commercial statistical software (SPSS 13.1 for Windows, SPSS). The Q-Q plots and the Shapiro-Wilk W-test were used to assess the normality of the data. Results are expressed as median and range.

3 | RESULTS

Criteria for inclusion in the study were met by 201 dogs. These dogs were of 57 different breeds. Most commonly represented were mongrels (n = 37), Dachshunds (n = 15), Jack Russell Terriers (n = 15), Boxers (n = 11), French Bulldogs (n = 11), and Maltese dogs (n = 11). The study group consisted of 102 males (59 intact and 43 neutered) and 99 females (14 intact and 85 neutered). At the time of CT imaging, the dogs’ ages ranged from 4 to 14 years (median, 9 years), and their body weights from 4 to 66 kg (median, 13 kg).

The LDDST was performed in 12 dogs and UCCRs combined with PO HDDST in 189 dogs. Within the study group, 122 of the 201 dogs had >50% suppression after administration of dexamethasone (Figure 1A). The pituitary gland was enlarged in 64% (78/122) of these dogs (median P/B, 0.43 × 10⁻² mm⁻¹; range, 0.32-1.21 × 10⁻² mm⁻¹). In 2 of these 78 dogs, concurrent lesions in the adrenal glands were noted: 1 dog with an enlarged pituitary gland (P/B, 0.41 × 10⁻² mm⁻¹) and nonsuppressed plasma ACTH concentrations (59 and 72 ng/L) showed bilateral heterogeneous and irregular enlargement of the adrenal glands (19 and 15 mm thickness). In this dog, postmortem histopathology of the adrenal glands identified a hemangiosarcoma in 1 adrenal gland and a cortical carcinoma in the contralateral adrenal gland. In the other dog (P/B, 0.40 × 10⁻² mm⁻¹; Figure 2A), the right adrenal gland was asymmetrically enlarged (cranial pole, 14 mm; caudal pole, 7 mm thickness) with heterogeneous contrast uptake (Figure 2B). In this dog, the left adrenal gland was within normal limits (thickness, 7 mm; Figure 2C), and the plasma ACTH concentration of 142 ng/L was not suppressed, confirming a concurrent functional pituitary abnormality. In the remaining 44 of 122 (36%) dogs with >50% suppression after dexamethasone administration, the pituitary gland was of normal size (median P/B, 0.23 × 10⁻² mm⁻¹; range, 0.07-0.31 × 10⁻² mm⁻¹) and no adrenal lesions were detected. In 29 of these 44 dogs, displacement of the pituitary flush was visualized, which further demonstrated the pituitary origin of hypercortisolism in these dogs.

Dexamethasone resistance was present in 79 of the 201 dogs (Figure 1B). Among them, 47 dogs (59%) had an enlarged pituitary gland (median P/B, 0.43 × 10⁻² mm⁻¹; range, 0.32-1.21 × 10⁻² mm⁻¹) and 32 dogs (40%) had a normal pituitary gland (median P/B, 0.23 × 10⁻² mm⁻¹; range, 0.07-0.31 × 10⁻² mm⁻¹). In these dogs, the diagnosis was based on the adrenal images and nonsuppressed basal plasma ACTH concentration. ADH, adrenal-dependent hypercortisolism; nonsuppressible, circulating cortisol concentration or UCCR ≥50% compared to basal cortisol concentration in the LDDST or PO HDDST, respectively; PDH, pituitary-dependent hypercortisolism; pituitary enlarged, pituitary/body brain area (P/B) > 0.31 × 10⁻² mm⁻¹; pituitary nonenlarged, P/B ≤ 0.31 × 10⁻² mm⁻¹; suppressible: cortisol concentration <50% compared to the basal concentration after IV administration of 0.01 mg/kg dexamethasone in the low-dose dexamethasone suppression test (LDDST) or urinary corticoid-to-creatinine ratio (UCCR) <50% of the basal UCCR after PO administration of 0.1 mg/kg dexamethasone (high-dose dexamethasone suppression test, HDDST).
(median P/B, 0.57 × 10⁻² mm⁻¹; range, 0.32-1.50 × 10⁻² mm⁻¹). In 39 of these 47 dogs, the adrenal glands showed only hyperplasia, indicating PDH. In the remaining 8 dogs (17%), 1 dog had bilateral and 7 dogs had unilateral concurrent adrenal lesions (ie, abnormal adrenal shape with heterogeneous contrast uptake and increased dorsoventral thickness), suggestive of AT. In the dog with an enlarged pituitary gland (P/B, 0.33 × 10⁻² mm⁻¹) and bilateral adrenal lesions, mineralization was present in both adrenal glands, with the right being asymmetrically enlarged (cranial pole, 8 mm; caudal pole, 12 mm thickness) and the left more symmetrical (cranial pole, 8 mm; caudal pole, 7 mm thickness). Of the dogs with unilateral adrenal lesions, the thickness of the contralateral adrenal gland exceeded 7 mm (median thickness, 11 mm; range, 8-15 mm), consistent with inappropriate and unregulated stimulation by ACTH from the pituitary gland. Histopathology was available in 1 dog and disclosed adrenocortical carcinoma in 1 gland and hypertrophy in the contralateral adrenal gland.

In the remaining 32 of 79 (41%) dogs in the dexamethasone-resistant group, the pituitary gland was not enlarged (median P/B, 0.24 × 10⁻² mm⁻¹; range, 0.09-0.31 × 10⁻² mm⁻¹). In 27 of these 32 dogs, adrenal lesions were present in 1 (n = 24) or both (n = 3) glands while the plasma ACTH concentration was suppressed (median, 8 ng/L; range, 1-33 ng/L), consistent with ADH. In the 24 dogs with unilateral adrenal lesions, the median thickness of the contralateral adrenal gland was 5 mm (range, 4-7 mm). Thoracic metastases were not visible in any of these dogs. In the remaining 5 of 32 dogs in the dexamethasone-resistant group, the pituitary gland was not enlarged and the adrenal glands were symmetrical with homogenous enlargement and normal corticomедullary distinction. Furthermore, the plasma ACTH concentration was not suppressed (median, 50 ng/L; range, 45-100 ng/L) confirming the diagnosis of PDH. In 1 of these 5 dogs, the pituitary origin of hypercortisolism was further demonstrated by an abnormal pituitary flush.

In the total study group of 201 dogs, PDH was diagnosed in 164 dogs (82%), ADH caused by unilateral AT in 27 dogs (13%), and concurrent pituitary and adrenal lesions in 10 dogs (5%). Among dogs with PDH, 70% (n = 115) had an enlarged pituitary gland (median P/B, 0.49 × 10⁻² mm⁻¹; range, 0.32-1.50 × 10⁻² mm⁻¹). Hypophysectomy was performed in 13 dogs and histopathology identified a pituitary adenoma in all dogs. Histopathology of AT was available in 18 dogs and identified an adenoma in 4 and a carcinoma in 14 dogs. In dogs with concurrent adrenal and pituitary lesions, no histopathology of both organs was available and the origin of the disease could not be confirmed. Dogs were treated medically with trilostane. Follow-up was available in 2 of 10 dogs, and they survived ≤6 months.

4 | DISCUSSION

Our study indicates the importance of advanced diagnostic imaging of the pituitary and adrenal glands in dogs with hypercortisolism to determine prognosis and choose the most optimal treatment option. Although in dexamethasone-resistant PDH pituitary enlargement is rather common, in our study 64% (78/122) of dogs with dexamethasone-suppressible PDH also had an enlarged pituitary gland. Ideally, the treatment in dogs with an enlarged pituitary gland is removal of the ACTH-producing adenoma by hypophysectomy.26 Otherwise, substantial enlargement of the pituitary gland may cause pressure on the brain, which could lead to neurological signs associated with the intracranial mass.5,36 Hypophysectomy, however, is available only at a few specialty centers, and most dogs with PDH are treated medically with trilostane.3 The relatively large percentage of dogs with an enlarged pituitary gland in our study indicates that CT imaging of the pituitary area may provide additional information on the prognosis and quality of life of dogs with hypercortisolism. Therefore, advanced diagnostic imaging is indicated not only in dogs treated by surgery but also before starting medical treatment.

In the dogs with dexamethasone-resistant hypercortisolism in our study, 44% (35/79) had adrenal lesions for which CT scan characteristics were suggestive of AT. Twenty-seven of these dogs were diagnosed with ADH, and in 8 dogs pituitary enlargement also was present. These 8 dogs presumably had concurrent pituitary and adrenal hypercortisolism, but the differentiation between a hormonally

FIGURE 2 Transverse CT images during single slice dynamic scanning of the pituitary gland and adrenal glands after IV administration of iodinated contrast medium in a 8-year-old spayed female mixed breed dog with suppressible hypercortisolism. The pituitary gland is enlarged with a pituitary/brain area 0.40 × 10⁻² mm⁻¹ (A). The right adrenal gland (open arrows) was asymmetrically enlarged (cranial pole, 14 mm; caudal pole, 7 mm thickness) with heterogeneous contrast uptake (B) and the left adrenal gland (arrow) was within normal limits (7 mm thickness; C).
active tumor and other pathology such as hyperplasia or a nonsecret-
ing tumor could not be made.27 Finding nonfunctional lesions is of
importance for the prognosis because a nonfunctional adrenocortical
lesion can be or become a malignancy and a nonfunctional pituitary
lesion can cause a mass effect. Pituitary enlargement in these dogs is
an important finding because in this 10% (8/79) of patients it would
have been missed if differentiation of the origin of the hypercortiso-
lism was based only on abdominal ultrasonography. Lack of advanced
imaging in dogs with concurrent pituitary and adrenal hypercortisolism
would lead to unsuccessful control of hypercortisolism by means of
adrenalectomy and an unrealistic estimate of the prognosis and qual-
ity of life. Dogs with concurrent pituitary and adrenal lesions in our
study were treated medically with trilostane. If a dog is treated medi-
cally, the effects of trilostane and mitotane on cortisol suppression
are well known,38,39 but the consequences of medical treatment on
PT growth still are largely unknown. There are indications that treat-
ment with trilostane leads to an increase in the size of the pituitary
gland, but these studies were performed in healthy dogs.40

The major aim of contrast administration in dogs with normal
P/B is to diagnose a pituitary microadenoma in a nonenlarged pitui-
tary gland.24,25 In our study, displacement of the pituitary flush was
found in 66% of dogs with normal P/B. A tentative explanation why
not all dogs with microadenoma had an abnormal flush is that, during
the single slice dynamic scanning, the wrong location was chosen
and consequently the pituitary flush was missed. Multiple slice
dynamic scanning series, which give a panoramic overview of the
enhancement of the pituitary gland and of the pituitary flush in place
and time, could identify the likely position of the pituitary adenoma
more precisely.24

Computed tomographic imaging of the adrenal glands is a sensi-

tive way of assessing adrenal structure, but the accuracy of adrenal
gland size measurements remains unclear.27 In CT investigations of
the adrenal glands, risk of miscalculation exists when the long axis of
the measured adrenal gland is not perpendicular to the transverse
view. This situation might be compensated by CT quantification of
adrenal gland volume and attenuation, but the advantage of this
method needs further validation in a patient population.28,29 For the
purpose of our study, the structure and symmetry of the adrenal
glands were of main interest and the only cutoff used was a >7 mm
thickness for an enlarged adrenal gland, measured from the cross-
sectional CT image. The 7 mm threshold has been adapted from
studies on ultrasonographic evaluation of canine adrenal glands.14,15
However, concordance between adrenal gland measurements on CT
imaging and ultrasonography has not yet been assessed. Another limi-
tation of our study is that the ACTH assay used has not been vali-
dated to discriminate between PDH and ADH. The applied cutoff
value of 40 ng/L has been adapted from previous studies, but misclas-
sification in some cases is possible.

The majority of dogs diagnosed with ADH in our study underwent
adrenalectomy and histopathology of the adrenal glands confirmed an
adrenocortical adenoma or carcinoma.34 In the remaining dogs with
ADH, another therapeutic intervention was chosen and adrenal histo-
pathology was not available. In these dogs, the diagnosis of AT was
supported by structural features, shape, asymmetry, attenuation, and
excessive size of the adrenal gland. The differentiation between
cortisol-secreting AT and pheochromocytoma, aldosteronoma, a meta-
static mass, or a nonfunctional AT cannot be made by diagnostic imag-
ing.31,32 In the dogs included in our study, the presumptive diagnosis
of adrenal hyperplasia and, because there was no clinical suspicion of
other adrenal pathology, no additional endocrine testing or fine-needle
aspiration biopsies were performed. Still, lack of adrenal histopathology
in some of the dogs is a major limitation of this study.

The differentiation between bilateral adrenal hyperplasia and
bilateral ATs is difficult.17,41 Such was the case in the 2 dogs in our
study with dexamethasone-suppressible hypercortisolism and adrenal
lesions. Although in the 1 dog, in which no histopathology of the adre-
nal glands was available, the nature of the adrenal mass remains
unknown, in the other dog, an adrenocortical carcinoma was con-
firmed. In general, dogs with PDH develop symmetrical bilateral adre-
ocortical hyperplasia.16,17 However, some have adrenocortical
nodular hyperplasia, in which 1 or both adrenal glands can have 1 or
many variably sized nodules. With time, it may be difficult to distin-

In the total group of dogs with hypercortisolism in our study, 82%
(164/201) were diagnosed with PDH and 13% (27/201) with ADH.
The dogs in our study were referred and therefore some selection
might have occurred compared to dogs with hypercortisolism pre-

In conclusion, concurrent adrenal and pituitary lesions were
present in 5% (10/201) of the total study group and in 10% (8/79) of
dogs with dexamethasone-resistant dogs. An enlarged pituitary gland
(P/B > 0.31 × 10−2 mm−1) was diagnosed in 70% (115/164) of dogs
with PDH. This finding implies that imaging of both pituitary and adre-
nal glands should be included in the diagnostic evaluation of every
dog with spontaneous hypercortisolism to obtain all the information
needed for estimation of the prognosis and choosing the optimal
treatment.

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CONFLICT OF INTEREST DECLARATION
Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE
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Authors declare no IACUC or other approval was needed.
HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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