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STANDARD ARTICLE

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

1 | INTRODUCTION

Spontaneous hypercortisolism or Cushing's syndrome is 1 of the most common endocrine disorders in dogs.[1] 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).[2] 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.[4,5] 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.[2,11,12] 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.[13] 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 $>10 \times 10^{-6}$ 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 ($P/B \leq 0.31 \times 10^{-2}$ mm^{-1}) from enlarged ($P/B > 0.31 \times 10^{-2}$ 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 dorsoventral 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.[14,30] Bilateral normal-sized 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 bloods 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

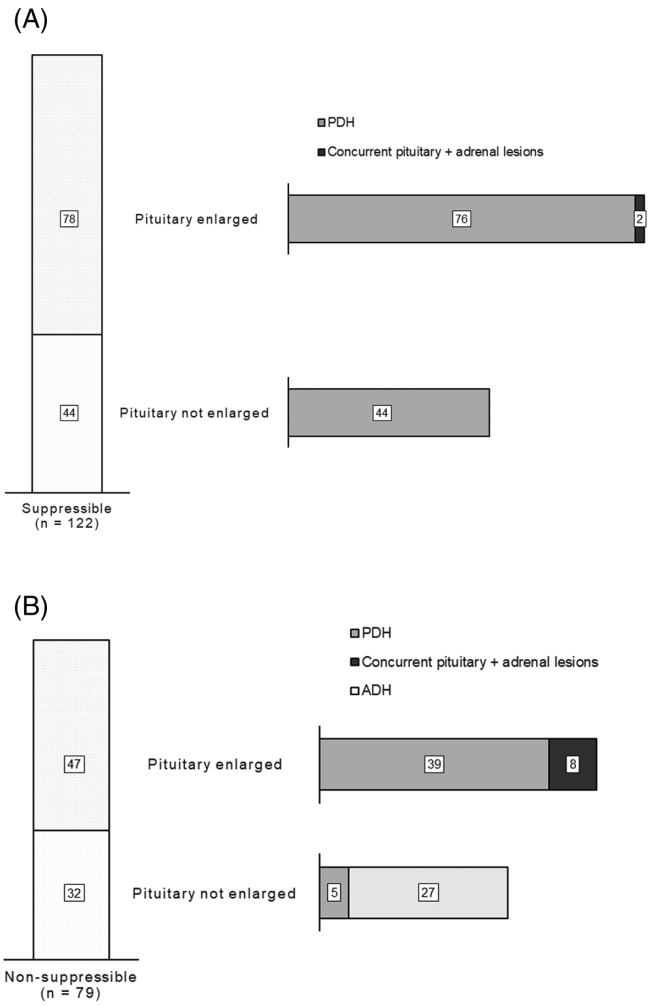

FIGURE 1 Endocrine and radiologic evaluation of the 201 dogs with spontaneous hypercortisolism included in this study. A, Among 122 dogs with suppressible hypercortisolism indicating PDH, the pituitary gland was enlarged in 78 dogs. In 2 dogs, concurrent adrenal lesions were present. B, Among 79 dogs with nonsuppressible hypercortisolism, pituitary gland was enlarged in 47 dogs. In 39 dogs solely PDH was diagnosed, whereas 8 dogs had concurrent adrenal lesions (adrenal glands >7 mm dorsoventral thickness and presented with heterogeneous structure and asymmetry, expansion into adjacent blood vessels, or both). The pituitary gland was not enlarged in 32 dogs. Five of them were diagnosed as PDH based on nonsuppressed basal plasma ACTH concentration and symmetrically enlarged adrenal glands with homogenous structure and no ingrowth in adjacent blood vessels. In the 27 dogs diagnosed with ADH, an adrenocortical tumor was confirmed by histopathology in 18 dogs. In the remaining 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/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)

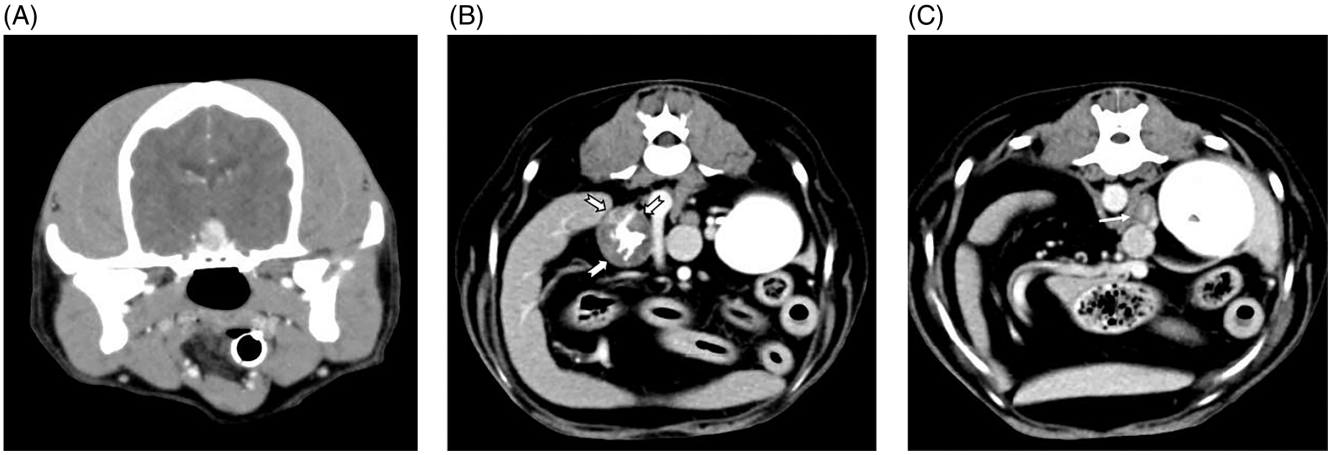

FIGURE 2 Transverse CT images during single slice dynamic scanning of the pituitary gland and adrenal glands after IV administration of iodinated contrast medium in a 8-year-old spayed female mixed breed dog with suppressible hypercortisolism. The pituitary gland is enlarged with a pituitary/brain area 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)

(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 corticomedullary 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

active tumor and other pathology such as hyperplasia or a nonsecreting tumor could not be made.[37] 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 hypercortisolism was based only on abdominal ultrasonography. Lack of advanced imaging in dogs with concurrent pituitary and adrenal hypercortisolism would lead to unsuccessful control of hypercortisolemia by means of adrenalectomy and an unrealistic estimate of the prognosis and quality of life. Dogs with concurrent pituitary and adrenal lesions in our study were treated medically with trilostane. If a dog is treated medically, 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 treatment 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 pituitary 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 sensitive 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 limitation of our study is that the ACTH assay used has not been validated to discriminate between PDH and ADH. The applied cutoff value of 40 ng/L has been adapted from previous studies, but misclassification 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 histopathology 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 metastatic mass, or a nonfunctional AT cannot be made by diagnostic imaging.[31,33] In the dogs included in our study, the presumptive diagnosis was hypercortisolism 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 adrenal glands was available, the nature of the adrenal mass remains unknown, in the other dog, an adrenocortical carcinoma was confirmed. In general, dogs with PDH develop symmetrical bilateral adrenocortical 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 distinguish between adrenal nodular hyperplasia and AT. It might even be hypothesized whether they occur independently of each other or the AT transitioned from initial hyperplasia.[42]

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 presented to first opinion practices, but the percentages of PDH and ADH in our study group resemble the percentages reported in the veterinary literature.[1,3]

In conclusion, concurrent adrenal and pituitary lesions were present in 5% (10/201) of the total study group and in 10% (8/79) of the dexamethasone-resistant dogs. An enlarged pituitary gland ($P/B > 0.31 \times 10^{-2}$ mm^{-1}) was diagnosed in 70% (115/164) of dogs with PDH. This finding implies that imaging of both pituitary and adrenal 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 (IACUC) OR OTHER APPROVAL DECLARATION

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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