Clinical Findings, Diagnostic Test Results, and Treatment Outcome in Cats with Spontaneous Hyperadrenocorticism: 30 Cases

S.Y. Valentin, C.C. Cortright, R.W. Nelson, B.M. Pressler, D. Rosenberg, G.E. Moore, and J.C. Scott-Moncrieff

Background: Spontaneous hyperadrenocorticism (HAC) is rare in cats. Clinical findings, diagnostic test results, and response to various treatment options must be better characterized.

Objectives: To report the clinical presentation, clinicopathologic findings, diagnostic imaging results, and response to treatment of cats with HAC.

Animals: Cats with spontaneous HAC.

Methods: Retrospective descriptive case series.

Results: Thirty cats (15 neutered males, 15 spayed females; age, 4.0–17.6 years [median, 13.0 years]) were identified from 10 veterinary referral institutions. The most common reason for referral was unregulated diabetes mellitus; dermatologic abnormalities were the most frequent physical examination finding. Low-dose dexamethasone suppression test results were consistent with HAC in 27 of 28 cats (96%), whereas ACTH stimulation testing was suggestive of HAC in only 9 of 16 cats (56%). Ultrasonographic appearance of the adrenal glands was consistent with the final clinical diagnosis of PDH or ADH in 28 of 30 cats (93%). Of the 17 cats available for follow-up at least 1 month beyond initial diagnosis of HAC, improved quality of life was reported most commonly in cats with PDH treated with trilostane.

Conclusions and Clinical Importance: Dermatologic abnormalities or unregulated diabetes mellitus are the most likely reasons for initial referral of cats with HAC. The dexamethasone suppression test is recommended over ACTH stimulation for initial screening of cats with suspected HAC. Diagnostic imaging of the adrenal glands may allow rapid and accurate differentiation of PDH from ADH in cats with confirmed disease, but additional prospective studies are needed.

Key words: Adrenal gland; Diabetes mellitus; Pituitary gland; Skin fragility.

Spontaneous hyperadrenocorticism (HAC) is a consequence of abnormally increased functional activity of the adrenal cortex. This disease classically (and most commonly) is associated with hypercortisolism in small animal companion species.[1–20] However, although well described in dogs, fewer than 100 cats with HAC have been described in the peer-reviewed veterinary literature, with the largest case series describing only 10 patients.[4] Although the typical clinical presentation of HAC in cats has been described,

Abbreviations:

ADH	adrenal-dependent hyperadrenocorticism
ALP	alkaline phosphatase
ALT	alanine aminotransferase
CT	computed tomography
DM	diabetes mellitus
DST	dexamethasone suppression test
HAC	hyperadrenocorticism
MRI	magnetic resonance imaging
PDH	pituitary-dependent hyperadrenocorticism
PU/PD	polyuria-polydipsia
USG	urine specific gravity

the relative frequency of associated history and physical examination findings, clinicopathologic abnormalities, diagnostic imaging findings, and treatment outcomes from a large case series are lacking.

The objectives of this retrospective case series were to determine the relative frequency of clinical, clinicopathologic, and diagnostic imaging abnormalities; determine the clinical performance of commonly used endocrine tests; and report outcome after various treatments in a large population of cats with spontaneous HAC. We hypothesized that the ACTH stimulation test would have poor sensitivity and specificity for the diagnosis of HAC in cats, whereas the DST would be more accurate for clinical use. We also hypothesized that adrenal gland ultrasonography and pituitary imaging (CT or MRI) would allow differentiation of adrenal-dependent (ADH) from pituitary-dependent (PDH) HAC in cats.

From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN (Valentin, Cortright, Scott-Moncrieff); the Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, CA (Nelson); the Department of Veterinary Clinical Sciences, The Ohio State University, Columbus, OH (Pressler); the Unité de Médecine Interne, Ecole Nationale Vétérinaire d'Alfort, Alfort, France (Rosenberg);and the Department of Comparative Pathobiology, College of Veterinary Medicine, Purdue University, West Lafayette, IN (Moore). Part of this study was presented as a poster at the 2012 ECVIM-CA Congress, Maastricht, Netherlands, in September 2012, and as a research abstract at the 2013 ACVIM Forum, Seattle, WA. Details of 2 cats included in this study have been previously published as part of another case series.

Corresponding author: J.C. Scott-Moncrieff, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, Purdue University, West Lafayette, IN 47907-2026; e-mail: scottmon @purdue.edu.

Materials and Methods

Case Identification

Cats with HAC were retrospectively identified at the Purdue University Veterinary Teaching Hospital (West Lafayette, IN), The Ohio State University Veterinary Medical Center (Columbus, OH), the University of California, Davis Veterinary Medical Teaching Hospital (Davis, CA), the University of Illinois Veterinary Teaching Hospital (Urbana, IL), Penn Vet's Ryan Hospital (Philadelphia, PA), and the Alfort University Veterinary Hospital (Centre Hospitalier Universitaire Vétérinaire d'Alfort, Alfort, FRANCE) by electronic medical record database search using the terms "feline," "hyperadrenocorticism," "adrenal hyperactivity," "Cushing's disease," and "adrenal mass" over variable time periods between 1990 and 2011. Five additional cats with suspected HAC from 4 additional referral institutions (Mississippi State University College of Veterinary Medicine Animal Health Center [Mississippi State, MS], Veterinary Hospital of the Cordeliers [Centre Hospitalier Vétérinaire des Cordeliers; Meaux, France], the Animal Medical Center [New York City, NY], and Upstate Veterinary Specialists [Greenville, SC]) were identified without systematic electronic medical database searches.

All medical records were reviewed by 2 coauthors (SV and CSM). Cats were considered to have been appropriately diagnosed with HAC if ≥1 of the following criteria were satisfied: (1) histopathologic confirmation of primary adrenocortical neoplasm with concurrent historical or physical examination abnormalities (eg, unregulated DM, dermatopathy); (2) concurrent histopathologic confirmation of adrenocortical hyperplasia and either intracranial diagnostic imaging or necropsy identification of a pituitary tumor; (3) ultrasound confirmation of bilaterally enlarged adrenal glands or an adrenal mass with supportive clinical signs and positive DST; (4) computed tomographic (CT) or magnetic resonance imaging (MRI) evidence of a pituitary mass with supportive clinical signs and positive DST. Cats that had been treated with exogenous glucocorticoids within 2 months of HAC diagnosis were excluded. Cats with sex hormone–producing adrenal tumors were also excluded.

Differentiation of PDH from ADH was determined by a combination of histopathology, advanced diagnostic imaging (CT or MRI), and ultrasound imaging. Cat signalment, owner-reported clinical signs, previous or concurrent medical diagnoses, physical examination findings, and results of selected diagnostic tests were extracted from medical records; all diagnostic tests were performed between 2 months before and 1 week after diagnosis of HAC, and before initiation of any treatment. Recorded diagnostic test results included: hematocrit, absolute total white blood cell, neutrophil, and lymphocyte counts, serum biochemistry profile, serum triglyceride concentration, total serum thyroxine concentration, urine specific gravity (USG) and results of urine cultures, indirect systolic blood pressure, results of diagnostic imaging (including standard abdominal radiography, abdominal ultrasonography, CT, and MRI), and adrenal and pituitary gland histopathologic abnormalities. Cats with indirect systolic blood pressure results >160 mmHg were defined as having systemic hypertension.

Endocrine testing protocols including formulation and dose of synthetic ACTH and dexamethasone used and times of blood collection were recorded. Reference ranges were not available from all testing facilities, precluding interpretation of results based on individual laboratory reference ranges. Instead, a post-ACTH serum cortisol concentration >14.9 μg/dL at any sampling time (30, 60, or 120 minutes) or a serum cortisol concentration >1.4 μg/dL at 4 hours, 8 hours, or both, post dexamethasone injection was considered consistent with a diagnosis of HAC.[20,21] DST serum cortisol concentrations 0.9–1.3 μg/dL were considered equivocal, and DST serum cortisol concentrations <0.9 μg/dL were considered to be within reference range.[17,20,21] Serum total thyroxine concentrations were interpreted using the reference ranges provided by the individual laboratories. Plasma endogenous ACTH concentrations <10.0 pg/mL were considered compatible with ADH and concentrations >12.0 pg/mL were considered compatible with PDH.[1]

Adrenal gland ultrasonographic descriptions (including adrenal gland width when available and subjective assessment of adrenal size) and abnormalities noted in other intra-abdominal organs, as well as documentation and description of a pituitary mass on CT or MRI, were recorded only when the study was performed by a board-certified veterinary radiologist. Normal ultrasonographic adrenal gland width was defined as 3.0–5.9 mm.[22] Treatment modality, resolution of clinical signs, change in insulin dose in response to treatment, and survival time from diagnosis were recorded when available.

Statistical Analysis

To calculate the specificity of the ACTH stimulation test, cats with nonadrenal illness were identified by searching the PUVTH medical records database for cats in which ACTH stimulation tests had been performed during 2007–2011. Cats were included if the record indicated a final diagnosis of an illness other than HAC to explain the clinical signs. Data collected included signalment, final diagnosis, and results of ACTH stimulation testing. ACTH stimulation test results were interpreted with the same criteria used for the cats with HAC.

Sensitivity was defined as the percentage of positive ACTH stimulation test results in the HAC cats. Specificity was defined as the percentage of negative ACTH stimulation test results in the cats without HAC. Sensitivity of adrenal ultrasound examination for differentiation of PDH versus ADH was defined as the percentage of equal-sized adrenal glands (for PDH) and unilateral adrenal enlargement with a small to normal-sized adrenal gland (for ADH). Confidence intervals (CI) of 95% were calculated for a binomial probability for each sensitivity and specificity reported, using the exact (Clopper–Pearson) method.

Median survival time (MST) was determined for all 30 cats, censoring the 8 cats lost to follow-up at discharge. Median survival time for the remaining 22 cats, censoring 15 cats lost to follow-up before death, was also reported.

Results

The final study population included 15 male and 15 female cats (age, 4.0–17.6 years [median, 13.0 years]) with pituitary-dependent (n = 27) or adrenal-dependent (n = 3) HAC. Cat breeds included 28 mixed breeds and 2 Maine Coon cats.

Clinical Findings

Owner-reported clinical signs and abnormal physical examination findings in cats with HAC included dermatologic lesions (n = 30 [100%]), PU/PD (n = 26 [87%]), polyphagia (n = 21 [70%]), abdominal distension (n = 20 [67%]), muscle wasting (n = 20 [67%]), lethargy (n = 14 [47%]), weight loss (n = 14 [47%]), and weight gain (n = 7 [23%]). Dermatologic lesions included thin skin (n = 21 [70%]), alopecia (n = 18 [60%]), skin lacerations (n = 17 [57%]), and dull, scaling, or seborrheic skin (n = 4 [13%]).

Concurrent Illnesses

The most frequently diagnosed concurrent illness was unregulated diabetes mellitus (n = 27 [90%]). Other final diagnoses noted in the medical records included pancreatitis (n = 9 [30%]), chronic kidney disease (n = 11 [36%]), bacterial infections (cutaneous abscesses, urinary tract infections, bacterial rhinitis, or bacterial cholangio-hepatitis) (n = 16 [53%]), heart disease (hypertrophic cardiomyopathy, n = 3 [10%], restrictive cardiomyopathy, n = 1 [3%]), and pancreatic adenocarcinoma (n = 1 [3%]). Only 1 cat had no concurrent disease, although a 2-week episode of transient DM had been noted several months before diagnosis of HAC. The length of time between diagnosis of DM and diagnosis of HAC ranged from 0 to 24 months (median, 4 months). Three of 16 cats (19%) with HAC were hypertensive; but, there was no evidence of end organ damage in any cat. Clinical signs in the 3 cats without DM at the time of HAC diagnosis included nonhealing cutaneous wounds (n = 1), weight loss, lethargy, cutaneous abscesses and anorexia (n = 1), and polyphagia and multifocal alopecia (n = 1).

Clinicopathologic Findings

Clinicopathologic abnormalities other than hyperglycemia included anemia (13/27 [48%] tested cats; median, 33.0%; range 17.2–46.9%), hypochloremia (less than reference range in 7/17 [41%] tested cats; median, 112 mmol/L; range 96–128 mmol/L), and hypertriglyderidemia in 5/7 [71%] tested cats; median, 403.0 mg/dL; range 54–1592 mg/dL), (Table 1). Total serum thyroxine concentration was measured in 25 cats and was within the reference range in 21 cats (84%) and below the reference range in 4 cats (16%).

Bacterial infections, either documented by culture or empirically antibiotic responsive, were reported in 15 cats with HAC and included pyoderma (n = 4), upper respiratory tract infection (n = 2), pyelonephritis (n = 2), tooth root abscess (n = 1), pancreatic abscess (n = 1), and suspected lower urinary tract infection (n = 6). Aerobic urine culture resulted in bacterial growth in 3 of 15 (20%) cats.

ACTH Stimulation Test Results

ACTH stimulation testing was performed in 16 cats with HAC. Synthetic ACTH products used included cosyntropin (n = 8),[a] tetracosactide (n = 2),[b] and ACTH gel (n = 2). Doses of 125 μg (n = 6), 250 μg (n = 1), 83 μg (n = 1), and 5 μg/kg (n = 2) were administered. The dose was not reported in 6 cats. One (n = 3), 2 (n = 10), or 3 (n = 1) post-ACTH blood samples were collected 30 minutes (n = 10), 60 minutes (n = 16), 90 minutes (n = 1), 120 minutes (n = 2), or some combination of these times post ACTH.

Pre-ACTH cortisol concentrations ranged from 2.9 to 12.8 μg/dL (median, 5.8 μg/dL). The 60-minute post-ACTH cortisol concentrations ranged from 3.19 to 27.4 μg/dL (median, 13.76 μg/dL). Nine of 16 (56%) ACTH stimulation tests were consistent with the diagnosis of HAC. The ACTH stimulation test was within reference range in all 3 cats with ADH.

Cats with Nonadrenal Illness

Twenty-one cats with nonadrenal illness were included in the study for specificity analysis. In this group, breeds included DSH cats (n = 13), Himalayan

Table 1. Selected clinicopathologic findings in 30 cats with hyperadrenocorticism.

Analyte	Median (range)	Number of Cats Tested	Number (%) Cats with Abnormal Results
Hematocrit (%)	33.0 (17.2–46.9)	27	13 (48)
Total WBC ($\times 10^3$/μL)	17.0 (3.9–37.0)	28	14 (50)
Neutrophils ($\times 10^3$/μL)	11.2 (3.1–25.7)	29	16 (55)
Lymphocytes ($\times 10^3$/μL)	0.86 (0.0–13.4)	28	15 (54)
ALT (IU/L)	67.5 (21–469)	28	8 (29)
ALP (IU/L)	59 (10–1180)	29	6 (21)
GGT (IU/L)	3 (0–10)	13	1 (8)
CK (IU/L)	232 (74–519)	10	1 (10)
Sodium (mmol/L)	151 (142–157)	17	1 (6)
Potassium (mmol/L)	4.5 (2.8–5.5)	17	5 (29)
Chloride (mmol/L)	112 (96–128)	17	7 (41)
Phosphorus (mg/dL)	4.3 (2.4–7.2)	18	4 (22)
Calcium (mg/dL)	9.3 (8.1–11.2)	17	1 (6)
Albumin (g/dL)	3.5 (3.0–4.6)	17	4 (24)
Globulin (g/dL)	3.8 (2.5–4.6)	17	3 (18)
Total bilirubin (mg/dL)	0.2 (0.0–5.8)	18	2 (11)
Cholesterol (mg/dL)	215 (82–2226)	24	9 (38)
Triglycerides (mg/dL)	403 (54–1592)	7	5 (71)
Urine specific gravity	1.027 (1.012–1.063)	19	7 (37)
Urine protein dipstick	1+ (neg − 3$^+$)	20	15 (75)

(n = 2), and 1 each of Burmese, Ragdoll, Siamese, Birman, Tonkinese, and Abyssinian. Thirteen cats were neutered males and 8 were spayed females. Median age at the time of adrenal evaluation was 8 years old (ranged from 1 year old to 16 years old).

The final diagnoses in the cats with nonadrenal illness were nonadrenal abdominal mass (n = 3), inflammatory bowel disease (n = 2), and 1 each of lymphoma, hyperthyroidism, liver failure, chronic kidney disease, pseudomonas gastroenteritis with diabetic ketoacidosis, protein-losing enteropathy, heart failure, idiopathic hypercalcemia, laryngeal paralysis, gastric mass, acute hepatic insult, restrictive cardiomyopathy, megacolon, pancreatitis, urolithiasis, polycystic liver, and DM.

Products used were either cosyntropin-Cortrosyn or tetracosactide-Synacthen. Pre-ACTH cortisol concentrations ranged from <1.0 to 7.9 μg/dL (median, 3.4 μg/dL), and the 60-minute post-ACTH cortisol concentration ranged from 3.2 to 20.1 μg/dL (median, 10.6 μg/dL). The 60-minute post-ACTH cortisol concentration was within the reference range in 17 of 19 30-minute samples, and in 18 of 21 60-minute samples.

Sensitivity and Specificity of the ACTH Stimulation Test

The calculated specificity at 30 and 60 minutes for the ACTH stimulation test was 89% (95% CI, 67–99%) and 86% (95% CI, 58–95%), respectively. The sensitivity of the ACTH stimulation test was 56% (95% CI, 25–75%) if all sampling times were considered, and 46% (95% CI, 20–70%) if only the 60-minute sampling time was evaluated.

Dexamethasone Suppression Test Results

Dexamethasone suppression tests were performed in 28 cats with HAC (Table S1). Dosages of 0.01 mg/kg (n = 1, 3%), 0.1 mg/kg (n = 16, 57%), or both (n = 4, 14%) were administered. When both doses were administered, the different doses did not result in differences in the interpretation of the results. The dose of dexamethasone was not recorded in 7 cats. Twenty-seven cats with HAC had inadequate suppression of serum cortisol concentration 8 hours after administration of dexamethasone and 1 was in the equivocal range (this cat's 4-hour sample was also equivocal; it had a definitive histopathologic diagnosis of adrenocortical carcinoma and had clinical signs consistent with HAC such as polyuria, polydipsia, polyphagia, abdominal distension, weight gain, muscle wasting, lethargy, alopecia, skin tears, and lack of regrowth of hair). Twenty-one of 26 cats with HAC had inadequate suppression of serum cortisol concentrations 4 hours after dexamethasone administration. Dexamethasone suppression test results were consistent with HAC in 25 of 25 cats with PDH and consistent with HAC in 2 of 3 cats with ADH (Table S1). Overall, 27 of 28 DST were consistent with HAC, and 1 was equivocal (this cat had ADH).

Differentiation of PDH from ADH

Differentiation tests performed in the 30 cats in this study included abdominal ultrasound examination in all 30 cases, measurement of endogenous ACTH concentration (n = 8), and advanced cranial imaging (n = 9). The final diagnosis of PDH or ADH was made by histopathology in 15 cats, histopathology and advanced cranial imaging in 6 cats, advanced cranial imaging alone in 3 cats, and abdominal ultrasound examination in 12 cats.

Diagnostic Imaging Results

Ultrasonographic adrenal examination was available in all 30 HAC cats. Subjective assessment of adrenal gland size by a board-certified radiologist was available for all cats, and objective measurements were available in 16 cats (15 with PDH: width range, 5.5–10.8 mm; 1 ADH: 9 mm nodule). In the 27 PDH cats, 22 had bilateral adrenomegaly, 3 had normal-sized adrenal glands bilaterally, and 2 had unilateral adrenomegaly, 1 with a normal-sized contralateral adrenal gland, the other without ultrasonographic visualization of the contralateral adrenal gland (PDH was confirmed by histopathology in both of these cats). All 3 ADH cats had ultrasonographically identified unilateral adrenomegaly. Of these, 1 had an ultrasonographically identified adrenal mass and 2 had unilateral adrenal gland enlargement (1 with a normal-sized contralateral adrenal gland, the other with a small contralateral adrenal gland). Therefore, the sensitivity of ultrasonography for differentiation of PDH (equal-sized adrenal glands regardless of their size) from ADH was 93% (95% CI, 78–99%). Other ultrasonographic findings included an enlarged, hyper- or hypoechoic liver in 14 cats, ultrasonographic evidence of pancreatic disease (eg, enlarged pancreas, hyperechoic pancreas, pancreatic nodules) in 8 cats, and renal changes in 9 cats (hyper- or hypoechoic renal cortices, pelvic dilatation, polycystic kidneys). Intracranial diagnostic imaging was performed in 9 cats. Pituitary adenomas were present in all 9 cats (CT imaging, 7 cats, MRI, 2 cats).

Endogenous ACTH Results

Endogenous ACTH concentration was measured in 8 PDH cats (range 10–1250 pg/mL) and was consistent with a diagnosis of PDH in 7 cats (range 28.8–1250 pg/ml; median, 865 pg/mL).

Histopathology Results

Histopathology reports were available in 15 cats (13 PDH and 2 ADH). Histopathologic evaluation of adrenal glands was performed in 14 cats. In 4 cats, the adrenal glands were removed surgically and in 10 cats were evaluated at necropsy. One ADH cat had a left-sided adrenocortical carcinoma, the other a left-sided adrenocortical adenoma, possibly a well-differentiated carcinoma. One PDH cat with a pituitary tumor found

on necropsy had no adrenal glands evaluated because of previous bilateral adrenalectomy; the original histopathology report was not available for review. Of the 12 other cats with PDH, 2 cats had unilateral adrenal hyperplasia because only 1 adrenal gland was identified and analyzed (these 2 cats had pituitary tumors), 1 cat had bilateral necrotizing adrenalitis (consistent with mitotane use), and the other 9 cats had bilateral adrenal hyperplasia. Histopathologic examination of 8 pituitary tumors was performed, of which 1 was a carcinoma and 7 were adenomas. Three adenomas were determined to be chromophobe adenomas of the cranial pituitary gland; the remaining 4 were not further characterized. Two cats with histopathologic diagnoses of bilateral adrenal hyperplasia did not have histopathology of the cranial pituitary gland reported. Additional relevant histopathologic findings included a pancreatic carcinoma in one of the ADH cats and a thyroid carcinoma with normal serum total thyroxine concentration in a PDH cat.

Treatment

Follow-up was available for 17 cats with PDH treated for HAC. Treatments included trilostane[c] (n = 9), mitotane[d] (n = 3), metyrapone (n = 2), radiation therapy (n = 3), ketoconazole (n = 1), and bilateral adrenalectomy (n = 3). Three cats were treated with multiple modalities. In 10 cats, no follow-up or treatment was reported after diagnosis of HAC. In the PDH cats, 9 were treated with trilostane[c] (4 cats ≤1 month and 5 cats 10, 12, 18, 21, and 21 months) and 3 of these cats are still alive and doing well at the time of writing.

The dosages used ranged from 0.5 to 12 mg/kg PO q24 h or q12 h. One cat was followed up for 21 months after diagnosis, and then lost to follow-up. One was euthanized 18 months after starting treatment attributable to chronic kidney disease. One cat treated with mitotane[d] (150 mg or 40.5 mg/kg once a day for 5 days, then once a week) survived 63 months and then was lost to follow-up. One of the 2 cats that underwent bilateral adrenalectomy was euthanized 11 months later attributable to acute renal failure; the other was euthanized during surgery. Of the 2 cats treated with metyrapone (250 mg PO q12 h), 1 was unresponsive and the other experienced improvement in clinical signs, but then was euthanized during surgery for adrenalectomy. Two of 3 cats with ADH underwent adrenalectomy. No follow-up was available for the ADH cats.

Two cats with concurrent DM and HAC no longer required insulin therapy after treatment with radiation therapy. Reduction in insulin dosage was required after treatment for HAC in 6 cats; 1 cat required only intermittent insulin administration. No change in insulin dose or frequency was reported in the 8 remaining cats. Median survival time of all 30 cats with HAC was 1 month. Median survival time for the 22 cases discharged with follow-up (of which 15 were censored) was 2.25 months.

Discussion

The most common presenting clinical signs for cats with HAC in this study were unregulated DM and dermatologic abnormalities. Therefore, the combination of dermatologic abnormalities and unregulated DM should prompt diagnostic testing for HAC. Other concurrent diseases were also common and may complicate and delay the diagnosis of HAC. Concurrent nonadrenal illness was the cause of death in 5 cats, whereas 10 died or were euthanized because of HAC (the remaining cats were either lost to follow-up or are still alive at the time of writing). The clinical presentation and clinicopathologic findings in the cats with HAC in this study were distinct from those observed in dogs with HAC.[23] Furthermore, hypertension was much less common than in canine HAC.[24] Seventy-five percent of dogs with untreated HAC are proteinuric and 86% hypertensive, whereas only 18% of the cats in this study were hypertensive.[24] Proteinuria was not documented in this study because many of the medical records did not contain either a complete urinalysis or a urine protein/creatinine ratio performed on a sample with no evidence of inflammation. Likewise, increased serum ALP and ALT activities were uncommon in this group of cats, except when concurrent pancreatitis or liver disease was present. Finally, unlike dogs with HAC, 70% of which have decreased serum total thyroxine concentration, the majority of cats with HAC had normal serum total thyroxine concentration.[25]

The specificity of the ACTH stimulation test was similar to that reported in the dog[26]; however, the sensitivity of the ACTH stimulation test for diagnosis of HAC in this group of cats was only 56%. Consequently, the ACTH stimulation test is not recommended as an initial diagnostic test in cats with suspected HAC. The ACTH stimulation test was least useful in cats with ADH, all of which had ACTH stimulation test results within the reference range.

We did not calculate the sensitivity of the DST for all 30 cats because a positive DST was part of the inclusion criteria for some cats. The majority of the DSTs in this study were performed using a 0.1 mg/kg dosage of dexamethasone.[27] This is the most commonly reported protocol in the cat because 20% of healthy cats do not suppress with 0.01 mg/kg dosage.[27,28] In this study, lack of cortisol suppression at either 4 or 8 hours after dexamethasone administration was considered diagnostic for HAC.[29] In the 1 case with equivocal results and an inverse pattern of suppression defined as lack of suppression at 4 hours and suppression at 8 hours, the cat had obvious clinical signs of HAC, and an adrenocortical carcinoma was confirmed histopathologically.

We could not evaluate the diagnostic accuracy of the urine cortisol-creatinine ratio, because it was not measured in any of the cats included in the study. It is likely, however, that this test would be difficult to interpret because studies have shown that concurrent disease causes an increased urine cortisol-creatinine

ratio in cats, and there was a high rate of concurrent diseases in this population of cats with HAC.[30,31]

Tests to differentiate ADH from PDH should be performed after diagnosis of HAC. Differentiation tests performed in this study included abdominal ultrasound examination, measurement of endogenous ACTH concentration, and advanced cranial imaging. Abdominal ultrasound examination performed by board-certified radiologists was accurate in differentiating PDH from ADH in most cases. Despite this, in 2 cats with PDH, unilateral adrenomegaly was identified. The contralateral adrenal in 1 cat was normal in size on ultrasound examination, which should have triggered a suspicion for PDH.[32] Measurement of endogenous ACTH was also useful for differentiation in the majority of cats in which it was performed. In 7 of 8 cats with PDH, the endogenous ACTH concentration was consistent with PDH. Unfortunately, special sample handling and processing are required for samples collected for measurement of endogenous ACTH and most commercially available assays have not been validated for cats, limiting routine use of this assay.[1,33] Advanced cranial imaging is useful in cats with suspected PDH to confirm the diagnosis of a pituitary tumor and to determine the size of the pituitary tumor.[1] In this study, a pituitary tumor was identified in all cats with PDH in which cranial CT or MRI was performed. Cranial imaging is required if treatment with radiation therapy or hypophysectomy is being considered.[6,34]

In our study, several treatment modalities were utilized. Five of 9 cats treated with trilostane had a positive and sustained (>1 month) response. This is consistent with the results of a previous study of 5 cats with HAC treated with trilostane.[7] Only 2 cats had resolution of DM with treatment of HAC in this case series, and both these 2 cats were treated with radiation therapy. One of them had also been treated with metyrapone before radiation therapy. Insulin requirements decreased in 5 medically treated PDH cats with no apparent association with medication used. A decrease in insulin requirement is an indicator of the adequacy of control of HAC. It has been suggested that resolution of DM in PDH cats treated with radiation therapy indicates that radiation therapy results in better disease control than medical therapy.[34]

This study did not include non–cortisol-secreting adrenocortical tumors of which several cases have been reported in the literature.[17–20] These cases may be even more challenging to diagnose because clinical signs are not always typical of HAC and lack of cortisol secretion means that ACTH stimulation test and DST results may be normal or suppressed.[19] A sex hormone panel may help identify these adrenocortical tumors.

Limitations of this study include its retrospective nature and lack of consistency in the diagnostic testing and treatment protocols. Also, we were not able to evaluate the sensitivity and specificity of the DST, because this result was included in the diagnostic criteria for diagnosis of HAC in some cats and because we were not able to identify enough cats with nonad-renal disease that had been tested using the DST. Furthermore, the large number of cases lost to follow-up limits the interpretation of treatment and prognosis.

In conclusion, cats with unregulated DM and dermatologic signs such as cutaneous fragility or thin skin should be evaluated for HAC. The DST using a dosage of 0.1 mg/kg should be the initial test performed, because the ACTH stimulation test has poor sensitivity for diagnosis of HAC. It does, however, have a role in monitoring response to medical treatment. Ultrasonographic evaluation of the adrenal glands, cranial imaging, and measurement of endogenous ACTH allow differentiation of ADH versus PDH in most cases. Additional studies are required to establish the diagnostic performance (positive and negative predictive value) of the DST, especially in the presence of other causes of unregulated DM. Subjectively, trilostane is the safest and most effective treatment option for PDH. Unilateral adrenalectomy remains the treatment of choice for ADH.

Footnotes

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Dexamethasone dose and cortisol concentrations at 4 and 8 hours after dexamethasone administration in 30 cats with HAC. Results in bold were interpreted as diagnostic for HAC. Doses listed as DST were cats in which the dose was unknown.