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A retrospective study of dogs with atypical hypoadrenocorticism: a diagnostic cut-off or continuum?

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Abstract

Objectives—To describe the clinicopathologic findings and outcome in dogs with atypical hypoadrenocorticism (Group 1) and dogs with suspected atypical hypoadrenocorticism whose post-adrenocorticotrophic hormone stimulation cortisol concentrations were greater than 55 nmol/L but below the laboratory reference interval (Group 2).

Methods—Medical records were searched to identify dogs diagnosed with hypoadrenocorticism between January 2004 and June 2014. Dogs were excluded if their Na:K ratio was less than 27 or if they had received prior therapy that could interfere with adrenocorticotrophic hormone stimulation testing.

Results—Forty dogs were included in Group 1 and nine dogs in Group 2. In Group 1, the most common biochemical abnormalities were hypoalbuminaemia (87%) and hypocholesterolaemia (76%). Of 35 dogs in Group 1 with follow-up biochemistry results, five (14%) developed electrolyte abnormalities at 2 to 51 months post diagnosis. Of seven dogs in Group 2 with follow-up, glucocorticoid therapy was discontinued in two dogs without return of clinical signs, four dogs were subsequently diagnosed with inflammatory bowel disease and one dog continued to have clinical signs despite glucocorticoid treatment.

Clinical Significance—Dogs with gastrointestinal signs and hypoalbuminaemia and, or, hypocholesterolaemia should be evaluated for atypical hypoadrenocorticism. Follow-up electrolyte monitoring is recommended because some will develop electrolyte abnormalities. Although dogs in Group 2 had a clinical presentation compatible with atypical hypoadrenocorticism, the diagnosis appears unlikely based on review of follow-up data. Dogs with equivocal adrenocorticotrophic hormone stimulation results should be evaluated for other underlying diseases such as inflammatory bowel disease. The use of endogenous adrenocorticotrophic hormone measurements in these dogs warrants investigation.

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Introduction

Hypoadrenocorticism (Addison's disease) is an uncommon endo-crinopathy in dogs resulting from insufficient glucocorticoid and mineralocorticoid production by the adrenal glands. In the majority of cases, primary hypoadrenocorticism is an immune-mediated process that causes destruction and subsequent fibrosis of the adrenal cortex. A range of clinical signs are associated with hypoadrenocorticism including lethargy, anorexia, vomiting and diarrhoea; signs can be chronic or present as acute, life-threatening illness. A low sodium:potassium ratio is the hallmark biochemical abnormality of hypoadrenocorticism. Hypoadrenocorticism most commonly affects young to middle-aged females. Several breeds are reported to be at increased risk, including the standard poodle, West Highland white terrier, soft-coated wheaten terrier, rottweiler, great Dane, Portuguese water dog, bearded collie and the Nova Scotia duck tolling retriever (Peterson *et al.* 1996, Oberbauer *et al.* 2002, Hughes *et al.* 2007).

A subset of dogs with hypoadrenocorticism, up to 32% in one report (Hughes *et al.* 2007), have glucocorticoid deficiency with normal sodium:potassium ratios at the time of diagnosis. These dogs are classified as having “atypical hypoadrenocorticism”. Published data on atypical hypoadrenocorticism in dogs is limited – only case reports and small case series (18 dogs) have been published (Lifton *et al.* 1996, Sadek & Schaer 1996, Hughes *et al.* 2007, Thompson *et al.* 2007).

The gold standard for diagnosis of hypoadrenocorticism is the adrenocorticotrophic hormone (ACTH) stimulation test. A post-ACTH stimulation cortisol level less than 55 nmol/L is consistent with the diagnosis (Peterson *et al.* 1996). However, this cut-off often differs from the lower limit of the laboratory reference interval, and dogs may have post-ACTH stimulation cortisol concentrations that are above 55 nmol/L but below the reference interval. To our knowledge, there are no studies evaluating dogs with clinical suspicion for hypoadrenocorticism and ACTH stimulation results that are subnormal, but do not meet the standard diagnostic criterion for hypoadrenocorticism.

The primary objective of this study was to characterise clinical signs, clinicopathologic abnormalities, response to treatment and outcome in a relatively large group of dogs with atypical hypoadrenocorticism. The secondary aim of this study was to describe the same clinical features and outcome in dogs with suspected atypical hypoadrenocorticism based on a post-ACTH stimulation cortisol concentration greater than 55 nmol/L, but below the respective laboratory reference interval.

Materials and Methods

Electronic medical records at the University of Minnesota were searched for dogs with the term “hypoadrenocorticism” in the diagnosis or problem list between January 1, 2004 and June 1, 2014. Dogs were excluded if there was a history of systemic, topical or inhaled glucocorticoid therapy within four weeks of diagnosis, if there was any history of mitotane, trilostane, selegiline or ketoconazole administration, or if a previous diagnosis of hyperadrenocorticism had been made. Dogs were also excluded if their sodium:potassium

ratio was less than 27 (Adler *et al.* 2007). Dogs that met the study criteria were subcategorised into two groups. Group 1 included dogs with a definitive diagnosis of hypoadrenocorticism based on a post-ACTH stimulation serum cortisol concentration less than 55 nmol/L. Group 2 included dogs with a presumptive diagnosis of hypoadrenocorticism made by a board-certified internist or internal medicine resident, based on history, clinical signs and post-ACTH stimulation serum cortisol concentration greater than 55 nmol/L, but less than the reference interval at the given laboratory. All ACTH stimulation tests performed before July 1, 2010 were performed by the University of Minnesota Veterinary Diagnostic Laboratory using the pre- and post-ACTH stimulation cortisol reference intervals of 13.8 to 110.4 nmol/L and 220.8 to 552.0 nmol/L, respectively. After that date, all ACTH stimulation tests were performed by Marshfield Laboratories using pre- and post-ACTH stimulation cortisol reference intervals of 27.6 to 138.0 nmol/L and 276.0 to 552.0 nmol/L, respectively. Both laboratories used a competitive immunoassay with enzyme-labelled chemiluminescent technology (Immulite® 1000, Siemens).

Medical records were reviewed, and the following information was collected: signalment, presenting clinical signs, concurrent illnesses, serum chemistry and complete blood count (CBC) abnormalities at the time of diagnosis (including sodium, potassium, chloride, glucose, cholesterol, albumin, haematocrit, neutrophils, lymphocytes and eosinophils), medical imaging (including radiographs and ultrasound), response to treatment and cause of death. For dogs with ultrasonographic evaluation of adrenal glands, “small” was defined as a left adrenal gland thickness less than 3.2 mm (Wenger *et al.* 2010). Follow-up, if not performed at the University of Minnesota, was obtained through review of veterinary records from the primary veterinary clinic managing the patient and telephone contact with owners. Descriptive statistics were performed. Data are reported as median (range) for all data, regardless of distribution, as the data spread in this study was considered to be more clinically relevant than standard deviations. Because of the small size of Group 2, inter-group statistical comparisons were not performed.

Results

Forty-nine dogs were included in the study. There were 40 dogs in Group 1; 38 of 40 had post-ACTH stimulation cortisol concentrations less than or equal to 28 nmol/L, and two dogs had concentrations of 33 nmol/L. There were nine dogs in Group 2; the median post-ACTH stimulation cortisol concentration was 171 nmol/L (range 94 to 223 nmol/L). Group 1 was comprised of eight Labrador retrievers, three standard poodles, two each of the following breeds, cocker spaniel, West Highland white terrier, Border collie, pug, English pointer, mixed breed and one each of 17 other breeds. In Group 1, there were 23 neutered males and 17 spayed females with a median age of 7.8 years (range, 0.83 to 14 years). Group 2 was comprised of three Labrador retrievers, and one each of the following breeds, soft-coated wheaten terrier, Anatolian shepherd, basset hound, Airedale terrier, standard poodle and Yorkshire terrier. In Group 2, there were two neutered males, one entire male and six spayed females. The median age of dogs in Group 2 was 4.0 years with a range of 0.5 to 10.2 years.

Table 1 summarises the presenting clinical signs for all dogs. One dog from Group 1 was not included in this table because the clinical signs at the time of presentation were not recorded. The most common clinical signs were lethargy (67%), anorexia (52%), vomiting (68%) and diarrhoea (56%). Three dogs had no overt clinical signs and were being evaluated for decreased albumin and cholesterol noted on routine health screening. Twenty-seven of the dogs in Group 1 (69%) and three of the dogs in Group 2 (33%) had a history of chronic illness defined as clinical signs beginning at least three weeks before diagnosis.

The biochemical and haematological abnormalities, where available, for Groups 1 and 2 are listed in Table 2. Only abnormalities that were present in greater than 10% of dogs from either group are listed. Hypoalbuminaemia and hypocholesterolaemia were the most common biochemical abnormalities in both groups and recorded in 87 and 76% of dogs in Group 1, respectively, and in 56 and 43% of dogs in Group 2, respectively. Of the 38 dogs in Group 1 with complete biochemical panels, only one (3%) did not have hypoalbuminaemia, hypocholesterolaemia or hypoglycaemia. In contrast, 33% (3 of 9) of the dogs in Group 2 with complete biochemical panels did not have any of these three abnormalities. The most common abnormalities on CBC in Group 1 were lymphocytosis (33%), anaemia (28%) and neutrophilia (25%); lymphopaenia was uncommon (5%). In Group 2, there were only one to two dogs with any given haematologic abnormality. Detailed medical information on the dogs in Group 2 is available as an online supplement (Appendix S1).

Thoracic radiographs were available in 15 dogs in Group 1 and two dogs in Group 2. There was no evidence of megaesophagus in any of the radiographic studies performed. Abdominal ultrasound reports were available in 16 dogs in Group 1 and five dogs in Group 2. In Group 1, 9 of 16 (56%) dogs had small adrenal glands ($< 3 \cdot 2$ mm left adrenal gland thickness). In two dogs, neither adrenal gland was identified. In the other 14 dogs in Group 1 with ultrasound reports, the median left adrenal gland thickness was 3.1mm (1.1 to 5.1mm). In Group 2, the five dogs that underwent ultrasonographic evaluation had normal adrenal size with a median left adrenal gland thickness of 3.5mm (3.2 to 6.3mm).

In Group 1, dogs had a median follow-up of $2 \cdot 3 \cdot 5$ months (range 0 to 74 months). Three dogs were lost to follow-up immediately after diagnosis. Thirty-five dogs had follow-up blood test results available for review. Of these, five (14%) developed electrolyte abnormalities at 2, 3, 4, 31 and 51 months after diagnosis with sodium:potassium ratios of 25.7, 22.5, 21.6, 15.7 and $2 \cdot 5 \cdot 7$, respectively. All dogs in Group 1 were on daily glucocorticoid supplementation (oral prednisone or prednisolone) at the time of last follow-up; the median maintenance dose could be determined for 37 dogs and was 0.14mg/kg/day (range, 0.03 to 0.39mg/kg/day). Glucocorticoid supplementation resulted in the resolution of hypoalbuminaemia and hypocholesterolaemia in 25 of 27 dogs (93%) and 23 of 25 (92%), respectively of dogs with follow-up blood test results. Clinical signs resolved in 30 of 31 (97%) Group 1 dogs for which clinical outcome data were available.

Two of the dogs in Group 2 had no follow-up data. For one, records were not available from the primary veterinarian, and the owner was unable to be reached. The other dog was euthanased less than a week after diagnosis for ongoing haematemesis, haematochezia and rectal prolapse. The median follow-up for seven dogs in Group 2 with data available was 24

months (range 10 to 77 months). None of these seven dogs developed electrolyte abnormalities at any time point. All dogs in Group 2 were initially treated with oral prednisone at a median initial dose of 0.27mg/kg/day (range 0.14 to 2.15 mg/kg/day). However, the median maintenance dose for glucocorticoid supplementation could not be determined for the seven dogs with follow-up data due to discontinuation of therapy or alternative diagnoses that affected glucocorticoid dose. Specifically, two dogs had their prednisone supplementation discontinued because of resolution of clinical signs. Both dogs continued in good health and had a repeat ACTH stimulation test performed; the results were similar to the initial test results with a post-stimulation cortisol concentration greater than 55 nmol/L but below the laboratory reference interval (223.6 and 256.7nmol/L, laboratory reference interval 276.0 to 552.0nmol/L). A third dog had gastric and duodenal biopsies consistent with inflammatory bowel disease (IBD), but this dog had resolution of clinical signs after a 3-week tapering course of prednisone (starting at 0.5 mg/kg/day) and no further therapy. Three additional dogs in Group 2 did not have resolution of clinical signs (including the only other dog receiving an initial glucocorticoid dose >0.5mg/kg/day) and were also subsequently diagnosed with IBD via endoscopically obtained gastric and duodenal biopsies. Clinical signs continued in the final dog with no alternate diagnosis reached. Hypoalbuminaemia (3) and hypocholesterolaemia (2) resolved in the dogs that had follow-up blood tests, but three of the five dogs that had these abnormalities at diagnosis were ultimately diagnosed with IBD and treated with immunosuppressive doses of glucocorticoids or other drugs.

Information regarding cause of death was available for 12 dogs in Group 1 and four dogs in Group 2. Five dogs in Group 1 were euthanased because of suspected neoplasia (liver mass, lymphoma, gastric carcinoma, pulmonary masses and histiocytic sarcoma), three because of neurologic disease (one with seizures and two with vestibular disease), one each because of gastrointestinal perforation, immune-mediated haemolytic anaemia, and, finally two because of age-related quality-of-life concerns (poor mobility). In Group 2, one dog was euthanased shortly after diagnosis for ongoing haematochezia and haematemesis, one for suspected sepsis, one for a bleeding splenic mass and one for age-related quality-of-life concerns (severe arthritis).

Discussion

This study describes the clinical signs, biochemical and haematologic abnormalities, and outcome, including the development of electrolyte abnormalities for 40 dogs with atypical hypoadrenocorticism (Group 1). To our knowledge, this is the largest population of dogs with atypical hypoadrenocorticism that has been reported in a single study. The study also describes a group of nine dogs that were presumptively diagnosed with atypical hypoadrenocorticism based on clinical presentation and post-ACTH stimulation cortisol concentrations between 55 nmol/L and the lower limit of the laboratory reference interval (Group 2).

In Group 1, there was a nearly even sex distribution (17 females and 23 males) in contrast to other published reports on dogs with classic and atypical hypoadrenocorticism in which up to 78% of the affected dogs were female (Sadek & Schaer 1996). In both dogs and humans,

females are generally believed to be more susceptible to developing immune-mediated diseases as a consequence of differences in their immune response (Brandao Neto & Carvalho 2014). The even sex distribution in this study could be a result of sampling error and may not accurately represent the true population of affected dogs.

Nearly all dogs in Group 1 had hypoalbuminaemia (87%), hypocholesterolaemia (76%) or both (72%); only two dogs in this group had normal albumin and cholesterol concentrations. The results of this study support the recommendation that dogs with gastrointestinal signs and either hypoalbuminaemia, hypo-cholesterolaemia or both, be screened for hypoadrenocorticism with a baseline cortisol concentration as a minimum (Lennon *et al.* 2007). It should also be noted that three dogs in this study were referred for hypoalbuminaemia and hypocholesterolaemia found on routine health screening without exhibiting signs of clinical disease.

Response to treatment has been sparsely mentioned in the previous literature on atypical hypoadrenocorticism. Lifton *et al.* (1996) reported that 10 of 18 dogs (56%) responded well to glucocorticoid supplementation alone. In our study, nearly all dogs in Group 1 showed improvement of their clinical signs, as well as resolution of hypoalbuminaemia and hypocholesterolaemia. Prognosis for these dogs was good; there was only one cause for euthanasia that could potentially be attributed to hypoadrenocorticism.

In Group 1, a minority of dogs, 14%, developed electrolyte abnormalities during the follow-up period. This finding is consistent with the 9% conversion rate identified by Thompson *et al.* (2007) and 11% by Lifton *et al.* (1996). The time until development of electrolyte abnormalities varied greatly, with two dogs converting years after the initial diagnosis of atypical hypoadrenocorticism. Based on these findings, dogs with atypical hypoadrenocorticism should have ongoing monitoring for the development of electrolyte abnormalities, although the frequency at which conversion occurs years after initial diagnosis may be low.

In Group 2, dogs were presumptively diagnosed with hypo-adrenocorticism by a small animal internist or resident, based on clinical presentation, absence of another diagnosis to explain the signs, and equivocal ACTH stimulation test results. These dogs do not fit the traditional definition of hypoadrenocorticism defined by a post-ACTH stimulation cortisol less than 55 nmol/L. However, they pose a diagnostic dilemma. Reference intervals are often established by testing a population of healthy animals and determining the range that encompasses 90 to 95% of the population, meaning that 5 to 10% of healthy animals will fall outside this range. Intervals can be calculated with greater than or equal to 40 subjects; lower numbers risk uncertainty, and it is inappropriate to use less than 20 subjects (Friedrichs *et al.* 2012). In contrast, the threshold for diagnosing a disease is statistically selected as the optimal cut-off value to maximise sensitivity, specificity or both, as through the use of a receiver operator characteristic curve and area under the curve. As such, an animal can have a value outside the reference interval but remain above or below the diagnostic threshold. An example of this would be the dogs in Group 2, which had subnormal post-ACTH stimulation cortisol levels but were above the classic cut-off value for hypoadrenocorticism of 55 nmol/L. In the case of hypoadrenocorticism, the 55 nmol/L post-

ACTH stimulation cortisol diagnostic cut-off did not originate from a receiver operator characteristic curve but was established based on concentrations observed in a population of 220 dogs with primary hypoadrenocorticism. All of those dogs had post-ACTH stimulation concentrations below 55 nmol/L, which equates to a sensitivity of 100%. It is important to note that these were dogs with electrolyte abnormalities; 96% of the dogs in that study had a sodium:potassium ratio less than 27 while none of the dogs in this study had a sodium:potassium ratio less than 27. To our knowledge, the optimal cut-off for dogs with atypical hypoadrenocorticism has not been separately determined and may be different. In Lifton *et al.* (1996) a post-ACTH stimulation cortisol concentration of 12.4 ± 2 nmol/L was used as the cutoff value for the diagnosis of atypical hypoadrenocorticism, but the study did not report the justification behind selection of this value. The median post-stimulation cortisol concentration in the 18 dogs included in the Lifton *et al.* study was 38.6 nmol/L, but the range went up to 121 ± 4 nmol/L. In other studies, dogs with post-ACTH stimulation cortisol concentrations greater than or equal to 55 nmol/L have been excluded (Sadek & Schaer 1996, Hughes *et al.* 2007, Thompson *et al.* 2007).

The absence of an established diagnostic cut-off value for atypical hypoadrenocorticism motivated the inclusion of the Group 2 dogs in this report. However, while performing the study, we uncovered a complicating factor. We learned that neither of the laboratories in this study had determined their own reference intervals for pre- and post-ACTH stimulation cortisol concentrations. Instead, the intervals were based on published ranges. One laboratory was unable to provide us with the citation for the publication they used. The other laboratory used a published range from a textbook on small animal endocrinology, but the origin of the range was not reported (Panciera & Carr 2006). We were unable to find a published report that has formally established a reference interval for post-ACTH stimulation cortisol using an immunoassay in greater than or equal to 40 healthy dogs. This is a limitation of the study, because we cannot estimate with high accuracy what portion of the healthy dog population would be expected to have post-ACTH stimulation cortisol concentrations below the reference intervals provided by the laboratories. However, we identified several publications that used the Immulite® chemiluminescent assay (Siemen) in small numbers of healthy dogs ($n = 20$) and reported comparable ranges (Singh *et al.* 1997, Cohn *et al.* 2008, Lathan *et al.* 2008, Ginel *et al.* 2012).

As discussed above, there are insufficient data to state that a post-ACTH stimulation cortisol concentration greater than or equal to 55 nmol/L rules out atypical hypoadrenocorticism, but there are several possible causes of equivocal results beyond those anticipated from normal variation in the population. Explanations include previous steroid use, errors in test administration and relative adrenal insufficiency. We excluded patients that had been treated with glucocorticoids within the previous four weeks to avoid any suppression of the hypothalamic-pituitary axis (Keppainen *et al.* 1982, 1989). Errors in test administration such as improper dosing and administration of synthetic ACTH used for stimulation testing cannot be entirely ruled out, but tests were conducted at the University of Minnesota by trained veterinary technicians. Critical illness-related corticosteroid insufficiency (Martin 2011) is, on the other hand, an important differential for the dogs in Group 2. While none of the dogs in Group 2 were critically ill, six of nine were hospitalised for varying degrees of

dehydration and anorexia and their concurrent illness could explain the blunted adrenal response to ACTH stimulation.

Another theory for the equivocal ACTH stimulation results is that these dogs may have been early in the course of their disease. However, a recent report of a dog with hypoadrenocorticism that developed electrolyte abnormalities before clinical evidence of a glucocorticoid deficiency demonstrated incremental decreases in adrenal function based on serial ACTH stimulation tests. This dog did not demonstrate signs consistent with glucocorticoid deficiency until its post-ACTH stimulation cortisol level was below less than 55 nmol/L (McGonigle *et al.* 2013). While this is a single case study, it suggests that clinical signs associated with glucocorticoid deficiency may not occur until cortisol levels fall below 55 nmol/L. Furthermore, two dogs in our Group 2 underwent repeat ACTH stimulation testing after discontinuation of glucocorticoid therapy and still had equivocal results. Progression would have been expected if these dogs were in early the course of their disease.

Ideally, the diagnosis of Group 2 dogs would have been based on a non-ACTH stimulation test gold standard. In human medicine, the diagnosis of hypoadrenocorticism is made through a combination of diagnostic tests. In addition to the ACTH stimulation test, diagnostic considerations include reduced adrenal size, paired serum cortisol and plasma ACTH concentrations, anti-cortex adrenal antibodies, and anti-steroid-21-hydroxylase antibodies (Husebye *et al.* 2014, Michels & Michels 2014). Of these additional diagnostics, the only one performed for the dogs in this study was ultrasonographic evaluation of adrenal size (16 dogs in Group 1 and five dogs in Group 2). While the majority of dogs in Group 1 (9 of 16) were reported to have small adrenal glands on ultrasound, none of the five dogs in Group 2 had abnormal adrenal gland size. Several recent studies support the use of endogenous ACTH levels and cortisol-to-ACTH ratios to diagnose dogs with hypoadrenocorticism (Lathan *et al.* 2014, Zeugswetter & Schwendenwein 2014, Boretti *et al.* 2015). However, the use of these diagnostics has not been evaluated in dogs with equivocal ACTH stimulation results. While adrenal antibody concentrations are used in the diagnosis of hypoadrenocorticism in human patients, they have not been well researched in dogs, and it is unknown if they would have a sufficient sensitivity and specificity to improve clinical diagnosis in dogs. Auto-antibodies against steroid synthesis enzymes have recently been evaluated in dogs (Boag *et al.* 2015). Dogs with hypoadrenocorticism were more likely to have P450 auto-antibodies than controls, but this test may have low sensitivity because only 24% of dogs with hypoadrenocorticism were positive for the auto-antibodies.

The term “atypical hypoadrenocorticism” can be misleading. Traditionally it has been used to describe dogs with hypoadrenocorticism that had no electrolyte abnormalities and so were suspected to have glucocorticoid deficiency with intact mineralo-corticoid activity. In a recent study by Baumstark *et al.* (2014), dogs with hypoadrenocorticism were found to have decreased baseline and ACTH-stimulated aldosterone levels regardless of presence or absence of electrolyte abnormalities. This study raises the question as to whether the term atypical hypoadrenocorticism should now only be used to describe dogs where: (1) secondary hypoadrenocorticism has been ruled out by endogenous ACTH; and, (2) mineralocorticoid activity has been quantified and determined to be preserved. With the current usage, the term simply describes dogs with hypoadrenocorticism that do not have

electrolyte abnormalities independent of underlying aetiology or mineralocorticoid activity. Endogenous ACTH and mineralo-corticoid activity were not evaluated in this study.

Ultimately, the diagnosis of atypical hypoadrenocorticism could not be proven in any Group 2 dog and appears to have been unlikely for most. Four dogs in Group 2 (44%) were later diagnosed with IBD by endoscopic biopsies. Hypoadrenocorticism and IBD could easily be confused given similar gastrointestinal signs and the frequent occurrence of hypoalbuminaemia and hypocholesterolaemia in the subset of IBD cases with protein-losing enteropathy. Additionally, it should be noted that the response of a few dogs in Group 2 to physiologic doses of glucocorticoids supplementation does not prove that they had atypical hypoadrenocorticism. In fact, these dogs continued to do well after glucocorticoid supplementation was discontinued thus arguing against a diagnosis of hypoadrenocorticism, which should require life-long supplementation. Thus, the noted improvement of clinical signs could have been temporally coincidental, the response of another corticosteroid-responsive condition, or placebo effect. Finally, none of the dogs in Group 2 subsequently developed electrolyte abnormalities, although the low conversion rate in Group 1 suggests that this could be a result of sample size. While it would seem highly unlikely that these dogs had concurrent atypical hypoadrenocorticism, adrenal lesions could not be excluded because necropsy was not available.

In summary, dogs with chronic gastrointestinal signs, hypo-albuminaemia and hypocholesterolaemia should be assessed for hypoadrenocorticism even if the classical electrolyte abnormalities of hyperkalaemia, hyponatraemia and hypochloridaemia are absent. If atypical hypoadrenocorticism is diagnosed, treatment is likely to be successful at resolving clinical signs and serum chemistry abnormalities. The prognosis for dogs with atypical hypoadrenocorticism is good and they are unlikely to die as a direct result of their disease. A small minority of dogs with atypical hypoadrenocorticism develop electrolyte derangements, and so periodic monitoring should still be considered even years following diagnosis.

Based on our retrospective review, dogs with compatible clinical signs and post-ACTH stimulation cortisol levels greater than 55 nmol/L but less than the given reference interval should be assessed for non-adrenal illness such as primary gastrointestinal disease. The diagnosis of atypical hypoadrenocorticism is unlikely in this subset of dogs; of the nine dogs in this study, four were subsequently diagnosed with IBD, three were weaned from glucocorticoids without relapse of clinical signs, and two did not respond to glucocorticoid therapy. Nevertheless, atypical hypoadrenocorticism could not be excluded completely. The use of endogenous ACTH measurement in this category of dog warrants further investigation. Furthermore, investigation of the optimal diagnostic cut-off for post-stimulation ACTH stimulation cortisol concentrations in dogs with atypical hypoadrenocorticism is also needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Presenting clinical signs for dogs with a definitive [Group 1, post-adrenocorticotrophic hormone (ACTH) stimulation cortisol <55 nmol/L] or presumptive (Group 2, post- ACTH stimulation cortisol 55 nmol/L but below the laboratory reference range) diagnosis of atypical hypoadrenocorticism

Clinical sign	Group 1 n = 39 N (%)	Group 2 n = 9 N (%)
Lethargy	29 (74)	3 (33)
Chronic clinical signs	27 (69)	3 (33)
Vomiting	25 (64)	8 (89)
Anorexia	23 (59)	2 (22)
Diarrhoea	22 (56)	5 (56)
Haematochezia	11 (28)	2 (22)
Weakness	10 (26)	0 (0)
Weight loss	7 (18)	1 (11)
Abdominal pain	4 (10)	1 (11)
Melaena	3 (8)	1 (11)
Polyuria	1 (3)	1 (11)
Polydipsia	1 (3)	1 (11)

Table 2
Biochemical and haematologic abnormalities in dogs with a definitive [Group 1, post-adrenocorticotrophic hormone (ACTH) stimulation cortisol <55 nmol/L] or presumptive (Group 2, post- ACTH stimulation cortisol ≥ 55 nmol/L but below the laboratory reference range) diagnosis of atypical hypoadrenocorticism

Biochemical abnormality (reference interval)	Group 1 N of total (%) Median (range)	Group 2 N of total (%) Median (range)
Hypoalbuminaemia (27 to 37 g/L)	34 of 39 (87) 22 (14 to 36) g/L	5 of 9 (56) 22 (14 to 34) g/L
Hypocholesterolaemia (3.7 to 9.7 mmol/L)	29 of 38 (76) 2.7 (0.65 to 8.3) mmol/L	3 of 7 (43) 4.5 (1.8 to 6.4) mmol/L
Hypoglycaemia (4.2 to 6.5 mmol/L)	14 of 40 (35) 4.4 (2.7 to 7.8) mmol/L	1 of 9 (11) 5.5 (2.0 to 6.5) mmol/L
Increased BUN (3.2 to 11.0 mmol/L)	4 of 40 (10) 7.1 (2.1 to 19.2) mmol/L	2 of 9 (22) 6.0 (4.3 to 25.7) mmol/L
Increased ALT (22 to 91 U/L)	7 of 39 (18) 55 (11 to 886) U/L	1 of 8 (13) 38.5 (16 to 109) U/L
Increased AST (16 to 44 U/L)	15 of 35 (43) 53.5 (18 to 383) U/L	1 of 6 (17) 29 (18 to 47) U/L
Increased ALP (8 to 139 U/L)	4 of 39 (10) 37 (13 to 210) U/L	0 of 8 (0) 29.5 (7 to 83) U/L
Increased HCO ₃ ⁻ (15 to 25 mmol/L)	0 of 33 (0) 19 (13.7 to 23.9) mmol/L	1 of 7 (14) 22.2 (18.5 to 28.7) mmol/L
Lymphopaenia (0.78 to 3.36×10 ³ /μL)	2 of 39 (5) 2.73 (0.37 to 8.12)×10 ³ /μL	2 of 9 (22) 1.42 (0.51 to 3.37)×10 ³ /μL
Lymphocytosis (0.78 to 3.36×10 ³ /μL)	13 of 39 (33) 2.73 (0.37 to 8.12)×10 ³ /μL	1 of 9 (11) 1.42 (0.51 to 3.37)×10 ³ /μL
Eosinophilia (0 to 1.20×10 ³ /μL)	8 of 39 (21) 0.62 (0 to 4.60)×10 ³ /μL	2 of 9 (22) 0.32 (0 to 3.24)×10 ³ /μL
Neutrophilia (2.1 to 11.2×10 ³ /μL)	10 of 39 (26) 6.40 (2.24 to 24.29)×10 ³ /μL	1 of 9 (11) 6.61 (4.21 to 15.80)×10 ³ /μL
Anaemia (37.5 to 60.3%)	11 of 39 (28) 39.7 (23.5 to 60.7) %	1 of 9 (11) 46.6 (28.1 to 51.3) %

BUN blood urea nitrogen, ALT alanine transaminase, AST aspartate transaminase, ALP alkaline phosphatase