Atypical Addison's Disease in the Dog: A Retrospective Survey of 14 Cases

Fourteen dogs diagnosed with Addison's disease and having atypical serum electrolyte levels are described. Seventy-eight percent were female, and most showed signs of inappetence, weakness, or vomiting. Ninety-three percent of the cases had either hyponatremia without hyperkalemia or normal serum electrolyte concentrations. Hemogram features were variable and were not useful in suggesting a diagnosis of hypoadrenocorticism. The results of this study show that normal or mild serum electrolyte changes in a dog with clinical signs compatible with Addison's disease should not exclude this diagnosis from consideration. Definitive diagnosis depends on the demonstration of inadequate adrenoocortical response to adrenocorticotropic hormone (ACTH) stimulation.

Introduction. Typical hypoadrenocorticism or Addison's disease results from insufficient production of glucocorticoid and mineralocorticoid hormones from the adrenal glands. Dogs with Addison's disease typically show clinical signs of lethargy, inappetence, vomiting, diarrhea, weakness, and weight loss-which often suggest more common disease such as renal, gastrointestinal, or various toxicological disorders. Characteristic laboratory abnormalities include hyperkalemia, hyponatremia, azotemia, mild metabolic acidosis, and a normal leukogram with or without lymphocytosis or eosinophilia. In some dogs, however, these typical laboratory abnormalities are not present; particularly, electrolytes may be normal or show changes in only one parameter. These atypical addisonian cases have been described infrequently in the veterinary literature, where in many instances (ref 1-3), the clinician initially must suspect the diagnosis of hypoadrenocorticism. The purpose of this report is to describe 14 cases of Addison's disease in dogs with atypical clinicopathological findings.

Materials and Methods.
The medical records data base at the Veterinary Medical Teaching Hospital at the University of Florida was searched for dogs diagnosed with primary, spontaneous hypoadrenocorticism from 1979 through June 1992. Different search parameters (i.e., hypoadrenocorticism, Addison's disease, adrenocortical insufficiency) were given in order to retrieve all diagnosed cases. Twenty-eight cases were reviewed, and 14 were selected for inclusion

in this study based on atypical electrolyte findings having one of the following patterns: 1) hyponatremia and normokalemia, 2) normonatremia and hyperkalemia, 3) normonatremia and normokalemia, 4) normal serum electrolytes with, eosinophilia and lymphocytosis, and 5) hypoglycernia with any of the findings in 1-4. The patients' signalments, histories, physical findings, and serum biochemistry results were determined prior to any therapeutic intervention. IN some cases, standardized laboratory values from the referring veterinarians were used. In each case, a definitive diagnosis was made by demonstrating a low-resting serum cortisol level of less than 2 mcg/dl, with a subnormal or negligible response to exogenous adrenocorticotrophic hormone (ACTH) administration of less than 4 mcg/dl, in accordance with a standard protocol (ref 4). A post ACTH cortisol level of 4 mcg/dl was chosen in order to avoid including any equivocal test results.

Table 1

Frequency of Clinical Signs Observed in 14 Dogs
with Atypical Addison's Disease

Clinical Signs	Frequency (%)
Inappetence	9 (64)
Weakness	7 (50)
Vomiting	6 (43)
Lethargy/depression	6 (43)
Diarrhea	4 (28)
Weight loss	3 (21)
Collapsed/hypovolemic	3 (21)
Stilted gait	3 (21)
Polyuria/polydipsia	1 (7)
Bradycardia	1 (7)

Results. Of the 14 cases included in this study, 11 (78%) were female; six were spayed and five were intact. The mean and median ages were 5.4 and 6 years, respectively, with a range from two to 20 years. No breed predilection was noted. The most common clinical signs were inappetence, weakness, vomiting, and lethargy/depression (Table 1). Duration of clinical signs before presentation ranged from 1 to 60 days, with an average of 21 days. A progressive course of illness was present in all 14 cases.

Seven (50%; case nos. 1, 2, 8-11, 14) cases had hyponatremia and normokalemia. Serum sodium concentrations ranged from 132.0 to 144.5 mEq/L, with an average of 137.6 mEq/L. Case No. 2 developed a more severe hyponatremia with a minimal rise in serum potassium level two weeks later.

One case (No. 6) had normonatremia and hyperkalemia. Case No. 9 initially had mild hypernatremia and normokalemia, but progressed to normonatremia with hyperkalemia on subsequent evaluation. Normal serum electrolytes were seen in four (28%; case nos. 3, 5, 7, 13) cases. Case nos. 4 and 12 initially had hypokalemia and normal serum sodium levels; the hypokalemia might have been due to excessive vomiting. Case no. 4 developed more typical electrolyte abnormalities three weeks later at the time of referral.

Normal leukograms were seen in four (31%; case nos. 5, 7, 11, 14) of 13 cases, despite clinical signs of illness. An eosinophilia was noted in three (21%; case nos. 3, 4, 6) cases, while a lymphocytosis was present in case nos. 6 and 8. None of these cases had any known cause of eosinophilia (e.g., parasites, allergies, infection, or cancer). Mild lymphopenia was surprisingly a more common finding than lymphocytosis, being present in six (46%; case nos. 1, 2, 4, 9, 10, 12) of the 13 cases. Only case no. 1 received glucocorticoids prior to blood collection for a hemogram. Interestingly, case no. 4 had both an eosinophilia and a lymphopenia.

Hypoglycemia was evident in three (21%; case nos. 1, 4, 6) cases. Each was associated with one of the following patterns: hyponatremia and normokalemia (case no.1); normonatremia and hypokalemia (case no.4); and normonatremia and hyperkalemia (case no.6).

The serum sodium-potassium ratios (27:1) were nearly normal in all cases, except in case nos. 1, 6, and 9, which were decreased only slightly. Thirteen of the 14 cases demonstrated low-resting serum cortisol concentrations with subnormal or negligible responses to exogenous ACTH administration. The precortisol sample for case no. 10 was unavailable. All data are summarized in Tables 2 and 3.

Table 2

Serum Biochemistry Test Results* in Dogs with Atypical Addison's Disease

Table 2 (Table too large for page)

Footnote: Breed of dog. 1 Chow chow; 2 German shorthaired pointer; 3 Dandy dinmont; 4 Mixed breed; 5 Rottweiler; 6 Samoyed; 7 Golden retriever; 8 Toy poodle; 9 Irish setter; 10 Shih tzu; 11 Weimaraner; 12 Great Dane; 13 Airedale terrier; 14 English pointer.

Reference ranges for lab normals:: sodium (Na+), 145-153 mEq/L; potassium (K+), 4.2-5.6 mEq/L; chloride (CP), 110-118 mEq/L; Na+/K+ ratio, >27; adrenocorticotropic hormone (ACTH) stimulation, preACTH <2 mcg/dl; postACTH >4 mcg/dl; glucose, 70-110 mg/dl; blood urea nitrogen (BUN), 8-28 mg/dl; creatinine, 0.5-1.5 mg/d

Sex: FS=spayed female; MC=neutered male; F=female; M=male

A few lab values were from the referring vet. See original article if interested.

The cortisol levels were before and after ACTH stimulation as described in the text.

Table 3

Leukogram Results from 13 Dogs with Atypical Addison's Disease

Table 3 (Table too large for page)

Discussion. The information derived from this retrospective study demonstrates that primary hypoadrenocorticism should not be excluded from the differential diagnosis when electrolytes are normal or involve change in only one parameter. Of the 14 cases in this report, 93% had either hyponatremia without hyperkalemia or normal serum electrolyte levels. Sodium-potassium ratios also were normal in 78% of the cases.

Young to middle-aged, female dogs made up the majority of cases in this study. This finding is similar to other reports where females constituted 68% to 79% of the diagnosed cases of Addison's disease(ref 3-5). The fact that

females more often are affected by immune-mediated disorders may help to explain their overrepresentation in cases of hypoadrenocorticism if autoimmune disease plays a role in its pathogenesis, as is found in humans. (Ref 7). Adrenocortical insufficiency resulting from autoimmunity has been demonstrated in three dogs with Addison's disease. Interestingly, 13 of the 14 dogs in this study are purebreds, causing one to consider the possible role of genetics in this syndrome.

Aldosterone's main site of action is at the nephron, where it promotes sodium and chloride absorption from the proximal renal tubule and sodium absorption by exchange with potassium at the distal tubule. Aldosterone secretion is influenced by the renin-angiotensin system and plasma potassium level. (Ref 9)Adrenocorticotropin has a comparatively minor and transient effect on a1dosterone secretion. In aldosterone-deficient states, sodium ion conservation and potassium and hydrogen ion excretion are impaired, resulting in hyponatremia, hyperkalemia, and a tendency toward metabolic acidosis. In mild aldosterone deficiencies, clinical evidence of disease may be inapparent until sodium intake is diminished or sodium loss increases.

In a study describing plasma aldosterone levels in normal and adrenopathic dogs, those with hypoadrenocorticism did not differ significantly in their basal plasma aldosterone levels when compared to normal dogs. (Ref 10) However, following ACTH administration, dogs with hypoadrenocorticism had no increases in their plasma aldosterone concentrations as compared to normal dogs. The authors explained this finding by suggesting that dogs with hypoadrenocorticism already were functioning at a maximum aldosterone secretion capacity and that disruption of this equilibrium during times of stress of illness could not be met with additional aldosterone reserves (i.e., aldosterone insufficiency existed) to restore homeostasis.

All 14 cases of this report had electrolyte concentrations on initial presentation which were atypical for Addison's disease, despite subsequently being diagnosed with hypoadrenocorticism. This finding suggests that the cases had minimal aldosterone reserves and therefore were limited in their ability to restore electrolyte balance in the face of illness. Case nos. 2 and 4 illustrate this point. As their disease progressed, causing marked hyponatremia and hyperkalemia, their aldosterone reserves (which initially were somewhat adequate) became insufficient and consequently could not help restore homeostasis.

Hypoglycemia was present in three (2 1 %) of the 14 cases. Other investigators have found the frequency of hypoglycemia to be similarly low, ranging between 8 and 37%. (ref 1,2,4,5). It is postulated that hypoglycemia occurs because of decreased gluconeogenesis resulting from cortisol deficiency. Its occurrence, however, is inconsistent and unpredictable.

Mild azotemia was present in 57% of the cases in this study. Urine specific gravities ranged from 1.035 to 1.056, suggesting that the azotemia most likely was secondary to dehydration. Hypercalcemia was not present in any of the cases, although it has been reported to occur in approximately 30 to 45% of cases with hypoadrenocorticism. (Ref 4, 11).

Hemograms were done on 13 cases, with variable results. Normal leukograms were present in 31% of the cases. Finding a normal leukogram in a dog that is ill is noteworthy, because a normal, stressed dog with adequate adrenocortical, function ideally would have a lymphopenia, eosinopenia, and mature neutrophilia. Therefore, an eosinophilia or lymphocytosis in an ill dog can be viewed as inappropriate and should prompt consideration of hypoadrenocorticism. The eosinophilia with concomitant lymphopenia in case no. 4 was unexplained but may have reflected hypersensitivity or a parasitic infection; however, both fecal flotation and heartworm antigen test results were negative. The leukocytosis in case nos. 2 and 8 might be attributed to epinephrine release, although this is not a consistent finding in the other 11 cases. This variability in leukogram findings has been reported similarly elsewhere. (Ref 3-5)

Conclusion. The signalments and clinical signs of the cases in this report are similar to other reported cases of Addison's disease. Their atypical serum electrolyte levels, however, make them unique and show that normal or mild alterations in sodium and potassium levels in a dog with clinical signs compatible with hypoadrenocorticism do not exclude this diagnosis from the differential list. Any suspicion of Addison's disease should prompt the clinician to do an ACTH stimulation test.

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