# Clinical features and heritability of hypoadrenocorticism in Nova Scotia Duck Tolling Retrievers: 25 cases (1994–2006)

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**Objective**—To evaluate the clinical features and heritability of naturally occurring hypoadrenocorticism in Nova Scotia Duck Tolling Retrievers (NSDTRs).

**Design**—Retrospective case series.

**Animals**—25 NSDTRs with hypoadrenocorticism.

**Procedures**—Questionnaires completed by owners of NSDTRs with hypoadrenocorticism and medical records from veterinarians were reviewed for information regarding diagnosis, age at diagnosis, concurrent diseases, age at death, and cause of death. Pedigrees were analyzed for heritability and mode of inheritance of hypoadrenocorticism (including complex segregation analysis of pedigrees of 1,515 dogs).

**Results**—On the basis of results of ACTH stimulation testing, hypoadrenocorticism was diagnosed in 16 female and 9 male NSDTRs (including 6 full siblings). Median age at diagnosis was 2.6 years; the diagnosis was made prior to 2 years of age in 11 dogs. Seventeen dogs had hyponatremia, hyperkalemia, or both, and serum electrolyte concentrations were within reference ranges for 8 dogs at the time of diagnosis. Median survival time after diagnosis for 4 dogs that died or were euthanized as a result of medical causes was 1.6 years. Heritability was calculated at 0.98 with no sex effect, and complex segregation analysis fit a major gene model with an autosomal recessive mode of inheritance.

**Conclusions and Clinical Relevance**—In NSDTRs, hypoadrenocorticism was diagnosed at an earlier age, compared with published reports of age at diagnosis among the general dog population. Among the study dogs, 32% had no serum electrolyte abnormalities at the time of diagnosis, and the disease appeared to have an autosomal recessive mode of inheritance in the breed. (*J Am Vet Med Assoc* 2007;231:407–412)

Hypoadrenocorticism is a clinical syndrome resulting from deficiency of glucocorticoids, mineralocorticoids, or typically both. The most common cause of hypoadrenocorticism in dogs is complete loss of adrenal gland cortical function, although selective destruction of the zona fasciculata resulting in glucocorticoid, but not mineralocorticoid, deficiency has been reported.[1-5] Glucocorticoid deficiency may also result from impaired secretion of ACTH by pituitary gland corticotrophs but is uncommon in dogs.[3-5]

Hypoadrenocorticism is most commonly diagnosed in young female dogs.[1,4,6] In 1 retrospective study[4] involving 225 dogs with hypoadrenocorticism, 71% were female and the median age at diagnosis was 4.0 years (25th to 75th percentile, 2.5 to 6.5 years). Breeds reported to be at increased risk for hypoadrenocorticism include Great Dane, Portuguese Water Dog, Rottweiler, Standard Poodle, West Highland White Terrier, Soft Coated Wheaten Terrier, Bearded Collie, and Leonberger.[4,7-11] The narrow-sense heritability of hypoadrenocorticism in Bearded Collies, Standard Poodles, and Portuguese Water Dogs has been estimated as 0.76, 0.75, and 0.49, respectively, with both sexes equally affected.[7-9] Narrow-sense heritability is a measure of how a trait or disease will respond to selection and is measured on a scale of 0 to 1. In Standard Poodles and Portuguese Water Dogs, hypoadrenocorticism is likely influenced by a major locus with an autosomal recessive mode of inheritance[8,9]; however, the mode of inheritance in Bearded Collies is less definitive.[7] Research is ongoing to determine the genes involved in hypoadrenocorticism in these breeds.[7-9,12]

The NSDTR is a relatively rare breed that was developed in Nova Scotia, Canada, to lure (toll) waterfowl to the shoreline and retrieve them for hunters. The breed was accepted into the AKC in July 2003, and AKC records indicate that 347 NSDTR puppies were registered in 2005.[13] Hypoadrenocorticism in 5 related

**Abbreviations**

| | |
|---|---|
| NSDTR | Nova Scotia Duck Tolling Retriever |
| AKC | American Kennel Club |
| HDR | Highest density region |

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NSDTRs was reported in 1997,[14] and a recent health survey of NSDTRs performed by the Toller Health Coalition identified hypoadrenocorticism in 12 of 1,180 NSDTRs.[15] At the time of diagnosis, the mean age was 2.35 years and the youngest age was 15 weeks. Four of the 12 affected NSDTRs died at a mean age of 3.25 years.[15] This information suggests a genetic basis for hypoadrenocorticism in NSDTRs. The purpose of the study reported here was to evaluate the clinical features and examine the heritability and mode of inheritance of naturally occurring hypoadrenocorticism in NSDTRs.

## Criteria for Selection of Cases

To recruit NSDTRs for the study, owners were solicited through notices placed in United States and Canadian NSDTR newsletters, a mass mailing conducted by the US NSDTR Club to all of its members, and the provision of a Web page within the US NSDTR Club Web site. Medical records of NSDTRs for which a tentative diagnosis of hypoadrenocorticism had been made were reviewed. For inclusion in the study, an ACTH stimulation test must have been performed and serum cortisol concentrations before and after ACTH administration had to be < 2.0 µg/dL (55 nmol/L). In addition, serum electrolyte concentrations had to be measured and dogs could not have a history of glucocorticoid or o,p'-DDD administration prior to performing the ACTH stimulation test.

## Procedures

The medical records of NSDTRs meeting the criteria for inclusion in the study were reviewed, and information including signalment, initial complaints, and results of diagnostic tests at the time of diagnosis of hypoadrenocorticism was collected. Concurrent diseases were also recorded. A written questionnaire was distributed to each owner to obtain additional information, including the dog's date of birth, dam and sire, coat color, white markings, and current health status and health problems of the dog and its parents, siblings, and offspring (if known).

**Data analysis**—Because diagnostic tests were performed by several commercial diagnostic laboratories, results were recorded as an absolute value for each variable and interpreted as greater or less than the reference limits provided by the corresponding commercial laboratory. The exception was ACTH stimulation test results. Serum cortisol concentrations before and after ACTH administration had to be < 2.0 µg/dL (55 nmol/L), regardless of the reference range provided by the commercial laboratory. For all results, the range as well as the 25th, 50th (median), and 75th percentiles are presented.

**Estimation of heritability**—For the objective of estimating heritability of hypoadrenocorticism in NSDTRs, a threshold model for the liability to disease was used as described previously.[9,16] This risk is assumed to be a function of many genes and the environment and is assumed to be normally distributed. When the value for a dog's risk of disease is > 0, the dog will express the disease. When the value is < 0, the dog will be unaffected. This process, where the behavior of the unseen value determines what is observed (affected or unaffected) when crossing an unseen point, is called a threshold model. In addition, a test of the effect of sex on the liability of hypoadrenocorticism was also tested through the likelihood ratio test. Calculations were implemented through a computer program[17,a] designed for likelihood optimization in quantitative trait analysis that incorporated binary trait analysis as described by Duggirala et al.[18]

**Complex segregation analysis**—Complex segregation analysis, developed by Bonney,[19] is intended to integrate Mendelian transmission genetics at a single locus with the patterns of covariance expected in polygenic inheritance. Lynch and Walsh[20] provided a more complete description of complex segregation analysis. Elston et al[21] outlined the criteria that must be satisfied before acceptance of the single major locus model to reduce the risk of false-positive declarations of a major locus model. Evaluation of the models necessary for complex segregation analysis was conducted with a Bayesian software package.[b] This program is an extension of a software package of subroutines for genetic analyses with Gibbs sampling[c] that was rewritten to accommodate complex segregation analysis in binary traits for pedigrees that include inbreeding.

The software selected to conduct the complex segregation analysis was built on a Bayesian foundation, involving the use of Monte Carlo Markov chains through a Gibbs sampler. Accordingly, point estimates of unknown variables were not derived but were estimates of the posterior density for unknown variables. The Bayesian software package was recently used to evaluate the contribution of a major locus to osteochondral diseases in pigs,[22] and a more complete outline of the Monte Carlo Markov chain approach is detailed in that report. A Gibbs sample of 5,000 was generated, beginning with the creation of 300,000 total samples, a burn-in (ie, how long to run the chain before keeping samples) of 50,000, and a sampling rate of every 100th Gibbs value. This process was repeated a second time to create 2 replicate chains. From the 5,000 Gibbs samples, the mean, SD, mode, and the upper and lower limits of a 95% HDR were computed for each of the unknown variables.

## Results

Information was obtained regarding 46 NSDTRs for which a tentative diagnosis of hypoadrenocorticism had been made. Twenty-one dogs were excluded because of a lack of adequate diagnostic information to meet the study criteria. Twenty-five dogs met the criteria for inclusion in the study. Of the 25 NSDTRs, 16 were from the United States, 8 were from Canada, and 1 was from Denmark. Six dogs were dead at the time of data collection for the present study. Among the 16 female NSDTRs, 9 were sexually intact and 7 were spayed at the time of diagnosis of hypoadrenocorticism; among the 9 male NSDTRs, 6 were sexually intact and 3 were castrated at the time of diagnosis of hypoadrenocorticism. Median age at diagnosis of hypoadrenocorticism was 3.0 years (range, 7.5 weeks to 10.5 years; 25th

percentile, 5.5 months; 75th percentile, 5.4 years). Six females and 5 males were < 2 years old, and 10 females and 4 males were > 2 years old.

Complaints reported by owners were consistent with hypoadrenocorticism and included lethargy (n = 16 dogs), inappetence (13), vomiting (12), shivering (6), weakness (5), weight loss (4), and diarrhea (3). Two owners were also concerned about perceived musculoskeletal pain in their dogs.

Abnormalities identified via CBCs performed in 17 NSDTRs included high Hct (n = 3), low Hct (1), leukocytosis attributable to neutrophilia (2), lymphopenia and eosinopenia (1), and eosinophilia (1; **Tables 1 and 2**). Hyponatremia, hyperkalemia, or both were identified in 17 dogs, and serum sodium and potassium concentrations were within reference ranges in 8 dogs. Additional abnormalities identified via serum biochemical analyses in the 17 dogs with serum electrolyte abnormalities included high BUN concentration (n = 15/15 dogs; median, 49 mg/dL; range, 27 to 109 mg/dL), hyperphosphatemia (11/15; median, 8.1 mg/dL; range, 6.8 to 13.7 mg/dL), hypercalcemia (9/15; median, 12.8 mg/dL; range, 11.3 to 14.2 mg/dL), hypoglycemia (1/14 dogs; 62 mg/dL), and hyperglycemia (1/14; 169 mg/dL). Additional abnormalities identified via serum biochemical analyses performed in 6 of 8 dogs without serum electrolyte abnormalities included high BUN concentration (n = 2 dogs; 27 and 40 mg/dL) and hyperphosphatemia (1; 7.9 mg/dL).

Results of the ACTH stimulation tests were consistent with hypoadrenocorticism in all dogs. In 17 dogs with serum electrolyte abnormalities, median serum cortisol concentrations pre- and post-ACTH administration were 0.3 µg/dL (8 nmol/L; range, 0.1 to 1.0 µg/dL [8 to 28 nmol/L]) and 0.4 µg/dL (11 nmol/L; range, 0.2 to 1.1 µg/dL [6 to 31 nmol/L]), respectively (Table 1). In 8 dogs without serum electrolyte abnormalities, median serum cortisol concentrations pre- and post-

Table 1—Results of serum biochemical and hematologic analyses in 17 NSDTRs with abnormal serum electrolyte concentrations at the time of diagnosis of hypoadrenocorticism.

| Test | No. of dogs assessed | Median | 25th to 75th percentile | Range | No. of dogs with value greater than reference limit (%) | No. of dogs with value less than reference limit (%) |
|---|---|---|---|---|---|---|
| Cortisol (µg/dL) | | | | | | |
| Pre-ACTH stimulation | 17 | 0.3 | 0.2–0.5 | 0.1–1.0 | 0 (0) | 17 (100) |
| Post-ACTH stimulation | 17 | 0.4 | 0.2–0.9 | 0.2–1.1 | 0 (0) | 17 (100) |
| Sodium (mmol/L) | 16 | 134.1 | 130.5–136.9 | 121–144 | 0 (0) | 14 (87.5) |
| Potassium (mmol/L) | 17 | 7.1 | 6.6–7.6 | 5.5–8.4 | 16 (94.1) | 0 (0) |
| Na:K ratio | 16 | 19.7 | 17.4–24.5 | 14.4–26.2 | 0 (0) | 16 (100) |
| Chloride (mmol/L) | 13 | 102 | 97–106.4 | 92–118 | 0 (0) | 9 (69.2) |
| BUN (mg/dL) | 15 | 49 | 43–64 | 27–109 | 15 (100) | 0 (0) |
| Phosphorus (mg/dL) | 15 | 7.4 | 6.9–10.8 | 4.64–13.7 | 11 (73.3) | 0 (0) |
| Glucose (mg/dL) | 14 | 89 | 71–110 | 61.8–169.3 | 1 (7.1) | 1 (7.1) |
| Calcium (mg/dL) | 15 | 11.9 | 11.4–12.9 | 10.5–14.2 | 9 (60.0) | 0 (0) |
| Hct (%) | 12 | 51.6 | 42.2–58.9 | 36.6–62.2 | 3 (25.0) | 0 (0) |
| WBCs (cells/µL) | 11 | 11,300 | 10,205–13,150 | 7,000–21,100 | 2 (18.2) | 0 (0) |
| Neutrophils (cells/µL) | 11 | 7,350 | 5,515–8,867 | 4,500–14,500 | 2 (18.2) | 0 (0) |
| Lymphocytes (cells/µL) | 11 | 3,032 | 2,750–3,848 | 1,695–5,400 | 0 (0) | 0 (0) |
| Eosinophils (cells/µL) | 7 | 580 | 305–622 | 70–904 | 0 (0) | 0 (0) |

Table 2—Results of serum biochemical and hematologic analyses in 8 NSDTRs with serum electrolyte concentrations within reference ranges at the time of diagnosis of hypoadrenocorticism.

| Variable | No. of dogs assessed | Median | 25th to 75th percentile | Range | No. of dogs with value greater than reference limit (%) | No. of dogs with value less than reference limit (%) |
|---|---|---|---|---|---|---|
| Cortisol (µg/dL) | | | | | | |
| Pre-ACTH stimulation | 8 | 0.2 | 0.2–0.6 | 0.1–0.9 | 0 (0) | 8 (100) |
| Post-ACTH stimulation | 8 | 0.2 | 0.2–0.6 | 0.1–0.9 | 0 (0) | 8 (100) |
| Sodium (mmol/L) | 8 | 148 | 145–151 | 142–153 | 0 (0) | 0 (0) |
| Potassium (mmol/L) | 8 | 4.8 | 4.7–5.1 | 4.0–5.3 | 0 (0) | 0 (0) |
| Na:K concentration ratio | 8 | 30.3 | 29.3–32.4 | 27.7–38.3 | 0 (0) | 0 (0) |
| Chloride (mmol/L) | 6 | 119 | 116–120 | 101–120.5 | 2 (33.3) | 0 (0) |
| BUN (mg/dL) | 6 | 24.2 | 21.0–28.6 | 19.9–40 | 2 (33.3) | 0 (0) |
| Phosphorus (mg/dL) | 6 | 4.6 | 3.9–5.3 | 3.1–7.9 | 1 (16.7) | 0 (0) |
| Glucose (mg/dL) | 6 | 86 | 80–114 | 33.5–138.2 | 1 (16.7) | 1 (16.7) |
| Calcium (mg/dL) | 6 | 10 | 9.5–10.3 | 9.2–11.0 | 0 (0) | 0 (0) |
| Hct (%) | 6 | 38.3 | 36.2–42.7 | 29.9–47.4 | 0 (0) | 1 (16.7) |
| WBCs (cells/µL) | 6 | 9,780 | 7,400–10,600 | 7,100–12,200 | 0 (0) | 0 (0) |
| Neutrophils (cells/µL) | 6 | 5,580 | 4,884–6,222 | 4,510–7,392 | 0 (0) | 0 (0) |
| Lymphocytes (cells/µL) | 6 | 2,293 | 1,910–3,220 | 864–3,550 | 0 (0) | 1 (16.7) |
| Eosinophils (cells/µL) | 6 | 248 | 190–760 | 96–3050 | 1 (16.7) | 1 (16.7) |

ACTH administration were 0.2 µg/dL (6 nmol/L; range, 0.1 to 0.9 µg/dL [3 to 25 nmol/L]) and 0.2 µg/dL (6 nmol/L; range, 0.1 to 0.9 µg/dL [3 to 25 nmol/L]), respectively (Table 2).

Three of 8 dogs with serum electrolyte concentrations within reference ranges initially subsequently developed hyponatremia and hyperkalemia and were treated with mineralocorticoids. One dog with no serum electrolyte abnormalities was treated with fludrocortisone acetate[d] until its death secondary to trauma. As a result, it was not possible to determine that dog's mineralocorticoid requirement. In 4 dogs, serum electrolyte concentrations were maintained within reference ranges with glucocorticoid replacement treatment alone and remained within reference ranges 2 years after hypoadrenocorticism was diagnosed in 2 of those 4 dogs. At the time of data collection, 3 of 25 dogs had been euthanized because of quality-of-life concerns and 1 dog was found dead. Median survival time since diagnosis of hypoadrenocorticism for the 4 dogs was 1.6 years (range, 1 to 5.3 years). Additionally, 1 dog was euthanized at the time of diagnosis and 1 dog died secondary to trauma 1.75 years after diagnosis of hypoadrenocorticism. Nineteen dogs were alive at a median of 1.75 years (range, 3 months to 5.25 years) after diagnosis of hypoadrenocorticism.

**Familial relationships**—Although all dogs in the study were related, 2 subsets of dogs with their immediate family members illustrate the transmission of the disorder (**Figure 1**). Three pairs of affected siblings were identified. Hypoadrenocorticism was diagnosed in full siblings at approximately the same age; the mean difference in age at diagnosis among full siblings was 8 months (range, 5 to 12 months). None of the affected dogs were bred after diagnosis of hypoadrenocorticism. Five females were bred before the diagnosis of hypoadrenocorticism was made, resulting in 9 litters and 44 offspring. One of those offspring developed typical primary hypoadrenocorticism at 6 years of age; glucocorticoid-deficient hypoadrenocorticism was diagnosed in that dam and its sibling at 10.5 and 9.75 years of age, respectively. Current health information was available for 29 of 43 parents of dogs affected with hypoadrenocorticism. Major medical diseases identified in the parents included hypothyroidism (n = 1 dog) and glucocorticoid-deficient hypoadrenocorticism (1, as described).

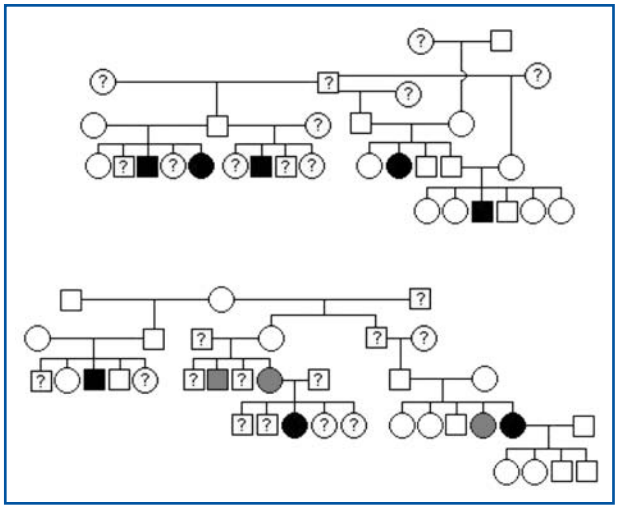

Figure 1—Pedigrees of 2 subsets of NSDTRs with hypoadrenocorticism included in a retrospective case series involving 25 hypoadrenocorticism-affected NSDTRs. Male dogs are represented by squares, and female dogs are represented by circles. Black symbols represent dogs with confirmed primary hypoadrenocorticism, and gray symbols represent dogs with confirmed glucocorticoid-deficient hypoadrenocorticism. Symbols with a question mark represent dogs for which a medical history was not available.

**Estimation of heritability**—Disease status information was available for 653 dogs (355 females and 299 males). With regard to hypoadrenocorticism, 628 dogs were considered unaffected and 25 dogs were affected. An additional 862 dogs without available medical histories (classified as hypoadrenocorticism-unknown) were included to build a pedigree of 1,515 dogs. In this pedigree, 1,247 dogs were inbred with a mean inbreeding coefficient of 0.17. The estimate of the heritability was 0.98 (SE, 0.08; $P < 0.01$). No significant sex effects were detected for the prevalence of hypoadrenocorticism in this sample population ($P = 0.50$).

**Complex segregation analysis**—Complex segregation analysis was performed (**Table 3**). In concert with the high heritability estimate, the results of this analysis indicated that the most plausible genetic explanation for this disease is the action of a single locus with an autosomal recessive mode of inheritance. This interpretation was based on the fact that the values for the major locus variance were much larger than those for the polygenic variance; the large values for the additive effect and dominance deviation were indicative of the recessive nature of the disease. For all variables assessed in the complex segregation analysis, the 95% HDR did not include 0, thereby indicating statistical significance of the major gene model. An equivalent analysis accommodating non-Mendelian transmission of the putative major allele was also performed (data not shown). Such an analysis, when evaluated through the 95% HDR, revealed an overlap of the estimated transmission probabilities with the expected Mendelian variables. Accordingly, the Mendelian model provides the best, most parsimonious fit for the hypoadrenocorticism data. The disease allele had an estimated frequency of 0.20 ± 0.11 in the NSDTR population examined.

Table 3—Marginal posterior means, modes, SDs, and limits to the 95% HDRs of model variables for hypoadrenocorticism in NSDTRs in a Bayesian mixed-inheritance model with a major locus and an autosomal recessive mode of inheritance.

| Value | Polygenic variance | Major locus variance | Additive effect | Dominance deviation | Frequency |
|---|---|---|---|---|---|
| Mean | 2.25 | 10.89 | 3.53 | –3.53 | 0.80 |
| Mode | 2.86 | 5.66 | 4.38 | –2.20 | 0.92 |
| SD | 0.61 | 6.04 | 1.33 | 1.33 | 0.11 |
| 95% HDR | | | | | |
| Lower limit | 0.30 | 2.79 | 1.38 | –7.74 | 0.31 |
| Upper limit | 3.16 | 23.55 | 8.17 | –0.98 | 0.97 |

## Discussion

In the present study, a relatively small, inbred population of NSDTRs with a suspected high prevalence of hypoadrenocorticism was examined. Six hundred sixty-five NSDTRs were registered by the AKC in 2004 and 2005,[13] the first 2 complete years that AKC registration statistics were available for NSDTRs. During that period, hypoadrenocorticism was diagnosed in 9 NSDTRs in the United States that were included in the present study. This suggests the incidence of hypoadrenocorticism in NSDTRs in the United States is approximately 1.4%. However, this incidence should be considered an estimate of the true incidence, in part because some NSDTRs in the United States may not be registered with the AKC and not all NSDTRs with hypoadrenocorticism may have received an appropriate diagnosis or been identified in our study. Interestingly, the estimate of 1.4% from the present study is similar to the incidence of 1.02% identified by the Toller Health Coalition in their health survey (1992 to 2002)[15]; both findings indicate that the genetic risk for hypoadrenocorticism in this breed is approximately 10-fold greater than that estimated for the general dog population (0.1%).[7]

Results of our study have suggested that heritability of hypoadrenocorticism in the group of NSDTRs evaluated is consistent with a single autosomal gene with a recessive mode of inheritance. Heritability analysis clearly determined that hypoadrenocorticism has a heritable component in these NSDTRs, and a heritability of this magnitude is itself suggestive of a segregating single gene of large effect.[23] This assertion was further supported by the complex segregation analysis, which revealed that the most plausible genetic explanation for this disease is the action of a single locus with an autosomal recessive mode of inheritance. Comparable analysis of a model for non-Mendelian transmission of the putative major allele revealed an overlap with the Mendelian transmission estimates, thereby indicating that the Mendelian model provided the best fit to the data (one of the criteria established by Elston et al[21]). Although the mode of inheritance cannot be completely defined until the underlying genetic mechanism is determined, breeders can select against this disease by assuming that hypoadrenocorticism is inherited as an autosomal recessive disorder.

Additionally, among siblings with hypoadrenocorticism, the diagnosis was made in a second sibling within 12 months of the diagnosis being made in the first sibling. This short interval could be attributable to a genetic predisposition within the litter for age of onset, an environmental effect of the litter, or increased owner awareness after the first diagnosis.

Among the NSDTRs in the present study, hypoadrenocorticism was diagnosed at an earlier age, compared with findings of previous studies[1,2,4,6] in the general dog population. In approximately 50% (12/25) of the affected NSDTRs, the diagnosis of hypoadrenocorticism was made when the dogs were < 2.5 years old, which represented the 25th percentile in the study by Peterson et al.[4] In addition, a diagnosis of hypoadrenocorticism was made in approximately equal numbers of sexually intact and spayed female NSDTRs and twice as many sexually intact as neutered male NSDTRs in our study. In contrast, Peterson et al[4] determined that sexually intact female dogs were at greatest risk for developing hypoadrenocorticism followed in decreasing order by neutered males, spayed females, and sexually intact males. The higher than expected number of sexually intact males with hypoadrenocorticism in the present study may be a reflection of the early age at diagnosis; 4 of the 9 males were < 7 months old at diagnosis, and only 1 had been neutered prior to diagnosis. Owners may not have neutered their dog because of the young age, the presence of nonspecific illness, or both. Owners also may have kept males sexually intact for future breeding purposes.

Clinical signs, abnormalities identified via routine clinicopathologic tests, and ACTH stimulation test results in the NSDTRs were similar to findings in dogs with hypoadrenocorticism in other studies.[1-2,4] Interestingly, 32% of the dogs in the present study had serum electrolyte concentrations that were within reference ranges at the time hypoadrenocorticism was diagnosed. Glucocorticoid-deficient hypoadrenocorticism has been previously reported in dogs[3-5] and is believed to result from inadequate ACTH secretion by the pituitary gland, selective destruction of the zona fasciculata of the adrenal gland cortex, or an early stage of hypoadrenocorticism wherein destruction of the zona glomerulosa and development of hypoaldosteronism has not yet occurred. Serum electrolyte abnormalities subsequently developed in 3 of the NSDTRs in the present study after the diagnosis of hypoadrenocorticism was established on the basis of results of ACTH stimulation testing, suggesting that the dogs were in the early stages of hypoadrenocorticism at the time of diagnosis. In contrast, serum electrolyte concentrations remained within reference ranges 2 years after the diagnosis of hypoadrenocorticism in 2 dogs. The etiology of the glucocorticoid deficiency in these 2 dogs is not known. Neither of these dogs had a history of prior glucocorticoid administration, endogenous plasma ACTH concentration was not determined in either dog, and both dogs were still alive. In light of the close family relationships among dogs with typical primary hypoadrenocorticism and those with glucocorticoid-deficient hypoadrenocorticism (including 1 dog with typical primary hypoadrenocorticism and its dam and the dam's sibling that had glucocorticoid-deficient hypoadrenocorticism), localization of glucocorticoid-deficient hypoadrenocorticism to the adrenal gland cortex seems possible. In future studies, measurement of plasma endogenous ACTH concentration in NSDTRs with hypoadrenocorticism and no serum electrolyte abnormalities should help clarify the etiology of the glucocorticoid deficiency in these dogs.

One limitation of the present study was the diagnosis of hypoadrenocorticism at multiple sites and by numerous veterinarians. Because this was a retrospective study, a standardized protocol for the ACTH stimulation test and measurement of blood cortisol concentrations at a single laboratory were not possible. Fortunately, the diagnosis of hypoadrenocorticism is based primarily on a single criterion, low baseline serum cortisol concentration and subsequent failure of serum cortisol concen-

tration to increase following administration of ACTH. This criterion was met for all NSDTRs included in the study. Detection of hyponatremia and hyperkalemia at the time of the ACTH stimulation test provided evidence for mineralocorticoid deficiency. Another limitation of the study was the assumption that all the NSDTRs that were classified as unaffected did not have hypoadrenocorticism. Presumably, some of these dogs may develop hypoadrenocorticism in the future. Our study involved analysis of a particular data set, and although the disease status of a small number of dogs may change and modify the analyses slightly, the significance of the study results indicated that those changes were unlikely to have altered the overall interpretation.

The incidence of hypoadrenocorticism in NSDTRs appears unusually high, and the disease is likely an autosomal recessive disorder. Owners and veterinarians should be aware of the risk of hypoadrenocorticism, the early age of onset, and the potential for results of serum electrolyte assessments to be within reference ranges at the time clinical signs of hypoadrenocorticism develop in NSDTRs. Further research focusing on identifying the gene mutation responsible for hypoadrenocorticism in NSDTRs and developing a genetic test to identify carriers are warranted.

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