Addison's Disease - A Better Understanding for Westie Owners

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Addison's or hypoadrenocorticism was identified in the West Highland White Terrier Club of America's 1999 Health Survey as a disease of concern for our breed. Since then, there have been several new developments associated with this disease. The Foundation co-sponsors with the Canine Health Foundation grants concerning the disease.

One grant is trying to develop a pre-clinical test for the disease and the second is trying to identify the genetic causation of the disease. Additionally, in 1998 Novartis Animal Health received FDA-approval for PERCORTEN-V™. PERCORTEN-V™ is the only product approved to treat canine hypoadrenocorticism. Novartis Animal Health is now heavily marketing the drug and hypoadrenocorticism to veterinarians. As this marketing program becomes successful, we should expect more Westies to be diagnosed with the disease. Information on this disease will help Westie owners understand the disease, its causes and treatment options.

History of Addison's Disease

Thomas Addison, an English physician, described the first case of hypoadrenocorticism in the mid-1800s.[1] He described the clinical syndrome to included anemia, lethargy, poor heart function, and gastrointestinal upset.[1] In the 1930's, glucocorticoids and mineralcorticoids became commercially available and were used to treat and save humans from this otherwise fatal disease.[1]

Hypoadrenocorticism occurs in humans at a rate of about one case per 100,000 people. There does not appear to be a bias with regard to race or age. In humans, hypoadreno-corticism is suspected to be the consequence of autoimmune destruction of the adrenal cortex. A genetic predisposition for autoimmune-mediated hypo-adrenocorticism has been confirmed in humans. Other suspected causes of hypoadreno-corticism in humans included infection, cancer, and disorders of the pituitary gland.

The first canine case of hypo-adrenocorticism was reported in 1953.[1] At that time, there were two compounds available for the treatment of Addison's disease. Unfortunately, neither was approved for use in dogs.

The frequency of hypoadreno-corticism in dogs greatly exceeds that seen for humans. It has been estimated that hypoadrenocorticism is 100 times from frequent in dogs than humans. Comparable to the disorder in humans, autoimmune destruction of the adrenal cortex has also been reported in dogs and may be related to the variable age of onset that ranges from 6 months to 8 years. Additionally, clinical signs of hypoadrenocorticism are diffuse, often resulting in a delay in obtaining a definitive diagnosis. Given that hypoadrenocorticism in humans reflects a genetic predisposition to autoimmune disease, dog breeders would benefit if a similar cause could be identified to exist for dogs.

What is hypoadrenocorticism?

Hypoadrenocorticism is a disorder characterized by the failure of the adrenal gland to produce sufficient hormones. The disease is classified in two forms based on the cause of the hormone deficiency. The two forms are primary hypoadreno-corticism and secondary hypo-adrenocorticism. In primary hypoadrenocorticism, the adrenal cortex becomes atrophied and is incapable of hormonal production. Secondary hypoadrenocorticism is attributed to an insufficiency of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland to stimulate adrenal cortex function.[1 2 3]

Because many of the clinical signs of Addison's Disease resemble those of other illnesses, it has been called "The Great Pretender."[3] It can be extremely frustrating and challenging for clients and clinical practitioners. Many dogs with the disease appear healthy and active. Sometimes the presenting signs are obscure and the subtle physical abnormalities induced by disease complicate in an already difficult case. Because of the difficulty in diagnosis until "classic Addisonian signs" occur, the Westie Foundation of America Board of Direction elected to participate in a research grant to develop a preclinical test for Hypoadrenocorticism in dogs.

What causes hypoadrenocorticism?

The common causes of primary hypoadrenocorticism include a variety of etiologies. An immune-mediated basis for the disease is suggested in cases where lymphocyte and plasma cell infiltration is identified in the adrenal cortex.[3] Other less common causes include: infections, hemorrhagic infarctions, granulomatous disease, metastatic neoplasia, trauma, and amyloidsis.

Secondary hypoadrenocorticism in small animals is usually due to excessive or prolonged administration of exogenous glucocorticoids. In these cases, normal adrenal function usually returns with a few months after gradual withdrawal of medication.

What is the Adrenal gland?

The adrenal gland is part of the endocrine system and is important in secreting hormones used for normal physiologic function as well as during stress.

It consists of a two-part structure located on the cranial pole of each kidney. The inner portion, the medulla, secretes the catecholamines adrenaline and epinephrine. The outer portion, the cortex consists of three distinct functional zones, each with a particularly secretory purpose.[4]

- The outer zona golmerulosa of the cortex is primarily involved with the synthesis and secretion of the mineralcorticoids, of which aldosterone is the most important.
- The middle zona fasciculate synthesizes and secretes glucocorticoids, of which cortisol is the most important.
- The inner zona reticularis of the adrenal cortex secretes primarily adrenal sex steroids (androgens and estrogens).

The Adrenal cortical function is often maintained even in the face of severe compromise.[1] It is estimated that the significant operational reserves of mammalian adrenal glands allow for up to 90% impairment before clinical signs appear. Furthermore, approximately 10% of animals with hypoadreno-corticism exhibit signs only after stressful situations. However, as glandular reserves

decline over time, an adrenal crisis (Addisonian crisis) may occur without an obvious precipitating event.[1] This is a life-threatening medical emergency requiring immediate and intensive treatment.

In up to 5% of dogs, other endocrine failure conditions - hypo-thyroidism, diabetes mellitus, and hypopar-thryoidism - often accompany a diagnosis of Addison's Disease.[5]

What do mineralcorticoids do?

Mineralcorticoids control electrolyte regulation and fluid balance.[1] Aldosterone, the primary adrenal mineralcorticoid, is important in Addison's Disease because of its specific effect on sodium, chloride, and water resorption. Also, aldosterone promotes potassium excretion, leading to extracellulary fluid volume expansion and increased blood pressure.[1]

Where mineralcorticoids are deficient, the ability to excrete potassium is diminished. This causes excessive sodium loss and hyperkalemia. Hyponatremia, in turn, leads to decreased circulating blood volume, resulting in prerenal azotemia, hypotension, dehydration, weakness, and depression. Hyperkalemia may also lead to myocardial toxicity.

What do glucocorticoids do?

Glucocorticoids, the most important of which is cortisol, affect nearly all body tissues.[1] Glucocorticoids regulate glucose, protein, and fat metabolism. They help inhibit inflammation.[1] Glucocorticoids are released in times of stress and are controlled by the hypothalamus (corticotrophin-releasing hormone) [CRH] and the pituitary gland (ACTH).[1]

Glucocorticoids deficiency can manifest as anorexia, vomiting, melena, lethargy, and weight loss. It can also predispose to hypoglycemia and results in impaired excretion of water free of sodium.[1]

How can you diagnose Addison's Disease?

You can use predisposing factors of breed, sex and age

In 1996, a retrospective medical records review of 225 dogs diagnosed with hypoadrenocorticism was conducted to evaluate the clinical and laboratory findings over a fourteen-year period. In the study, no specific risk factors for Addison's Disease could be identified; however, results showed there to be some correlation with age and breed, and a predisposition in females.[6]

The West Highland White Terrier was identified in this study as a breed with greater risk of developing Addison's Disease.

This study reported that there was a somewhat higher incidence of Addison's Disease in the four- to seven-year age group (average age at diagnosis was reported as 4.3 to 5.4 years). Then, as dogs age beyond seven to ten years, the odds ration approaches the level of the one-to four-year age group. Dogs younger that one year are the least likely to be diagnosed with hypoadrenocorticism.[6]

You can use clinical signs

Addison's Disease is a chronic disease with a wide range of clinical signs and symptoms.

Several of the more frequently observed signs, such as lethargy, weakness, and dehydration, mimic those of many other common diseases. Additionally, clinical signs are intermittent and often described as "waxing and waning." 5 Signs may vary between the chronic case and the acute crisis. In some dogs with chronic hypoadrenocorticism, only a few, mild intermittent clinical signs may be observed. However, the dog in acute Addisonian crisis may exhibit signs that are quite severe and life threatening.

Obtaining a through medical history is crucial in identifying hypoadrenocorticism. Sudden episodes of the more common signs, such as vomiting, diarrhea, and weakness, may occur and quickly resolve with fluid and/or glucocorticoids therapy. However, over time, a repeated pattern of these signs develops which may suggest progressive adrenal insufficiency.

Clinical signs and physical findings of hypoadrenocorticism[1 - 6]

Most commonly found

- Depression/lethargy
- Weakness
- Dehydration
- Vomiting
- Diarrhea
- Weight loss

May be present

- Melena
- Hematemesis
- Polyuria/polydipsia
- Anorexia
- Bradycardia
- Weak pulse
- Slow capillary refill
- Hair loss

Less often reported

- Hypothermia
- Shaking/tremors
- Painful/sensitive abdomen

Many dogs, due to the subtle and intermittent nature of the clinical signs with Addison's disease, go undetected until they are presented in crisis. At this point, the veterinarian faces a medical emergency with a severely weak dog that is in hypovolemic shock.[1,2] Approximately one-third of dogs in Addisonian crisis are presented with bradycardia due to hyperkalemia.[2] This is an

important distinguishing factor in hypoadrenocorticism, as hypovolemia from other causes is usually associated with tachycardia.[2]

The absence of a distinct set of clinical signs for hypoadrenocorticism contributes to the complexity of the disease. Also, the nonspecific nature of abnormalities induced by Addison's Disease can sometimes mask the actual condition. Therefore, in addition to a thorough medical history and physical examination, the veterinarian must rely on more advanced methods of diagnosis, including laboratory screening.

The clinical signs of Addisonian crisis

- Severe Weakness/depression
- Hypovolemic shock
  - Pale mucous membranes
  - Prolonged capillary refill time
  - Dehydration
- Bradycardia/arrhythmias
- Acute collapse

Laboratory test

Confirmation of primary hypoadren-ocorticism is achieved through laboratory analysis. Laboratory test must include a complete blood count (CBC), a serum chemistry profile with an electrolyte panel, and a serum cortisol concentration. A urinalysis can additionally be helpful in supporting the diagnosis. Dogs with adrenal insufficiency often have a urine specific gravity less than 1.030.[1]

Although a CBC is a valuable reference tool, there may be only minimal changes seen in the hypoadrenal dog.[1,2,3] The lack of a stress luekogram, which one would expect to see in an ill dog, should raise the suspicion of hypoadrenocorticism.[2] In dogs with hypoadrenocorticism, the common hematological findings include lymphocytosis and eosinophilia. Often a normocytoic, normochromic, non-regenerative anemia is present, which can be masked by dehydration.[1] If dehydration exists, an increase packed cell volume may be seen.[1,2]

The chemistry profile also may be unremarkable; however, electrolytes are key indicators of insufficient adrenal function. Most hypoadrenal dogs have a sodium/potassium ration of less than 20:11 (serum sodium is usually < 140 milliequiv-alents per liter (mEg/L), potassium is usually 6.0 mEq/L2) although not all hypoadrenal dogs will show these classic electrolyte alterations. Also, electrolyte levels alone cannot differentiate between primary and secondary hypoadrenocorticism.[1,2]

Frequently, hypoadrenocorticism is misdiagnosed as renal failure due to the similar laboratory profiles found in both diseases (i.e. hyponatremia, hyperkalemia, and hypochloremia). Response to fluid therapy can be used as an indicator; the azotemia associated with Addison's Disease often completely resolves with rehydration, while only a partial response is observed in cases of primary renal failure.[2]

The most accurate and reliable laboratory tool for a definitive diagnosis of hypoadrenocorticism is the ACTH stimulation test.[1] This is a relatively simple assay includes collecting blood samples

both before and after ACTH injections. Serum cortisol levels are compared and a positive diagnosis may be made when the concentration is undetectable or remains low after ACTH stimulation.

In cases where electrolyte values are normal, endogenous plasma ACTH concentrations can distinguish primary from secondary hypoadrenocorticism. This only possible when the blood sample is collected before the administration of glucocorticoids. [1,2,5] If glucocorticoids are necessary (e.g. in emergency cases), dexamthasone is the drug of choice because it does not interfere with the ACTH stimulation test.[2] A high endogenous ACTH level indicates primary disease, (i.e. normal pituitary gland functioning), with the lesion in the adrenal gland. Normal values for endogenous ACTH are between 20 picograms per milliter (pg/ml) and 100 pg/ml. In dogs with primary hypoadreno-corticism, levels as high as 554 pg/ml to 4950 pg/ml have been reported.[1]

In addition to utilizing laboratory data for the means of diagnosis, electrolyte levels also are monitored throughout the course of treatment, and are essential for determining dose adjustments of treatment and/ or supplemental steroids.

What is the treatment of choice for Addison's Disease?

PERCORTEN-V™ is indicated for use as replacement therapy in dogs with primary adrenocortical insufficiency.

It is an injectable aqueous solution containing the pure mineralocort-icoid, desoxycorticosterone pivalate (DOCP), a long-acting insoluble ester of desoxycorticosterone acetate (DOCA), and is administered intramuscularly as microcrystalline depot where the crystals dissolve slowly and are absorbed over time.[4]

How is maintenance achieved in dogs with Addison's Disease?

Because dogs with hypoadrenocort-icism require continuous treatment for the rest of their lives, regular monitoring is necessary to maintain adequate control of the disease.

Although a safe and efficacious dose of PERCORTEN-V™ has been established, some dogs may require dose adjustments throughout their treatment, a common practice in hormonal therapy. In order to measure the response to therapy, several repeat serological test are performed at regular intervals. These frequent reassessments allow the veterinarian to properly adjust the dose of PERCORTEN-V™, supplemental steroids, or both, if necessary to affect a positive outcome.

The most critical laboratory indicators of proper PERCORTEN-V™ dosing are electrolytes. During the initial 2 to 3 months of PERCORTEN-V™ therapy, electrolytes should be checked at day 14 and day 25. Dosing frequency may be adjusted based on these results. Once the dog is stabilized, repeat electrolyte analysis should be completed every 3 to 4 months.

The most common cause for treatment failure is insufficient supplemental glucocorticoids administration. In times of stress additional amounts of supplemental corticosteroids may be required. Signs of cortisol deficiency include profound depression, vomiting, and diarrhea.[4]

Is Addison's Disease in dogs inherited?

Anita M. Oberbauer, PhD and her colleagues at the University of California, Davis, CA are researching the heritability and mode of inheritance for hypoadrenocorticism in Bearded Collies. They reviewed the medical records and pedigrees of 636 Bearded Collies diagnosed with hypoadrenocorticoid phenotypes. Dogs were classified as affected by hypoadrenocorticism or unaffected. Phenotypic and pedigree data were analyzed. Heritability was estimated by use of Bayesian statistical methods. Regressive logistic models for complex segregation analysis were used to characterize mode of inheritance.

They found that the heritability of hypoadrencocorticism was estimated to be 0.75 with both sexes affected with equal probability. Evaluation of the pedigrees did not support a Mendelian autosomal dominant mode of inheritance. They were not convinced that there was sufficient evidence from the complex segregation analysis that a single locus of large effect on hypoadrenocorticism exists.

They did conclude that hypoadren-ocorticism in Bearded Collies is highly heritable. Although they have yet to determine the precise genetic mechanism responsible for inheritance of the disorder, they recommend breeding decisions must include consideration of the genetic likelihood of passing on this disease to offspring of dams and sires.[7]

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[6] *Peterson ME, Kintzer PP, Kass PH. Pretreatment clinical and laboratory findings in dogs with hypoadrenocorticism: 225 cases (1979-1993). Journal of the American Veterinary Medical Association, 1996; 208: pp 85-91.*

[7] *Anita M. Oberbauer, PhD, American Journal of Veterinary Research, 2002; 63:643-647.*

