Addison's Disease (Hypoadrenocorticism)

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Date Published: 01/01/2001
Date Reviewed/Revised: 04/24/2019

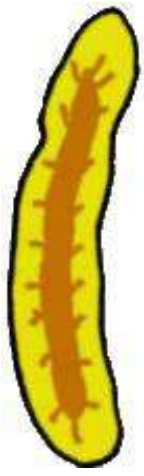
Adrenal Hormones

Kidneys are located at the level of the lower back and the adrenal glands (shown in yellow) sit atop the kidneys. Graphic by MarVistaVet

The adrenal gland is so named because it is located just forward of the kidney (renal means kidney). The center of the gland is called the medulla and the outer area is the cortex. While both areas produce hormones, Addison's disease concerns the hormones produced by the cortex; these hormones are called corticosteroids.

Corticosteroids are the hormones that enable us to adapt physiologically to stress. The glucocorticoids (such as cortisol and related synthetics, prednisone, dexamethasone and numerous others) act on the mechanics of sugar, fat, and protein metabolism. They gear the metabolism towards the preparation of burning, rather than storing, fuels so as to be ready for a fight or flight situation.

The mineralocorticoids (such as aldosterone and related synthetic fludrocortisone acetate) influence the electrolytes sodium and potassium. As a general biological rule, where there's sodium or salt, there's water. When the mineralocorticoids circulate as part of the fight or flight preparation, sodium is conserved in anticipation of blood loss so that there will be extra fluid in the vascular compartment (spare blood). When sodium is conserved, potassium is lost as part of the biological balance. This whole picture of fat mobilization, sodium conservation, and all this fight or flight preparation is far more complex than can be reviewed here but the bottom line is:



Cut surface of adrenal gland (the outer layer, in yellow, is the cortex). Graphic by MarVistaVet

Corticosteroid hormones are needed to adapt to stressful situations and without these hormones, even small stresses could lead to physiologic disaster.

Hypoadrenocorticism (Addison's Disease) is a Deficiency in Corticosteroid Hormones

In animals with Addison's disease, there is a deficiency of the corticosteroid hormones. It is unusual to discover the direct cause of this deficiency unless the patient is taking medications that disrupt adrenal balance (like ketoconazole, Lysodren or trilostane) but, fortunately, the disease can be managed by giving corticosteroid hormones even if the cause of the deficiency is unknown.

Clinical Signs

Patients are usually young (age four to five years) but any age dog can be affected. (This disease can occur in cats but is very rare.) There is a genetic predisposition for Addison's disease in the standard poodle and bearded collie. Female dogs are affected twice as often as males.

At first signs are vague: listlessness, possibly some vomiting or diarrhea. The dog just does not seem to feel right but not in an obvious way and may seem more or less normal most of the time as symptoms wax and wane with stress. This vague waxing and waning goes on and on with the dog never really getting fully sick but never staying well either. Eventually, the disease comes to a head in a phenomenon known as an Addisonian crisis. The animal collapses in shock due to his inability to adapt to the caloric and circulatory requirements in stress. Blood sugar may drop dangerously low. Potassium levels soar and disrupt the heart rhythm because there is not enough conserved sodium to exchange for potassium. Heart rate slows, arrhythmias result. The patient may not survive this episode.

About 30% of dogs with Addison's disease are diagnosed at the time of an Addisonian crisis. Approximately 90% of the adrenal cortex must be non-functional before clinical signs are observed.

Making the Diagnosis

Because it can present with a variety of symptoms, Addison's disease has earned the medical nickname "The Great Imitator." You would think that you could simply look for an increase in potassium and/or drop in sodium on a basic laboratory blood panel, but it turns out spot checks of electrolyte values like this are not reliable enough for a diagnosis of Addison's disease.

Classically, veterinarians are presented with a young animal in shock. There is usually no history of trauma or toxic exposure so general treatment for shock is initiated. This consists of rapid administration of fluids (usually lactated ringers solution, which has little potassium and a moderate amount of sodium) plus some glucocorticoids. By coincidence, this also happens to be similar to the specific treatment for Addison's disease so that often the patient simply recovers without the veterinarian really knowing why.

The blood panel will come back showing elevated kidney parameters (BUN and creatinine) and thus with the elevated potassium is suggestive of acute kidney failure, a condition with an extremely poor prognosis. The veterinarian may become suspicious of another diagnosis as the patient will respond well to fluids and most kidney failure patients do not respond as well.

Addison's disease may appear in more unusual ways. Inability to maintain normal sugar levels (ultimately manifesting as a seizure disorder) may be strongly suggestive of an insulin-secreting pancreatic tumor but before a major abdominal surgery is planned, it is important to test for Addison's disease.

Similarly unexpected, regurgitation of undigested food due to abnormal nerve function in the esophagus (a condition called megaesophagus) can ultimately be caused by Addison's disease. Of course, Addison's disease can also manifest with chronic waxing and waning diarrhea and/or poor appetite ,which would suggest a gastrointestinal problem such as inflammatory bowel disease. Before investing in the expense and potential anesthetic risk for endoscopy and intestinal biopsy, a screening test to rule out Addison's disease is prudent.

The only definitive test for Addison's disease is the ACTH stimulation test. The patient receives a dose of ACTH, the pituitary hormone responsible for the releasing corticosteroids in times of stress. A normal animal will show elevated

cortisol in response to ACTH while an Addisonian has a hormone deficiency and therefore has no corticosteroids to respond with. This lack of response is diagnostic for Addison's disease; however, a false positive may be obtained if corticosteroids have been used to treat the crisis prior to the test. Of all the commonly used corticosteroids, only dexamethasone does not interfere with the assay for cortisol; if any other steroid has been used, the test will not be valid for at least a couple of days.

A screening test can be performed in that a resting cortisol level can be tested without doing the entire ACTH stimulation test. If the resting cortisol is higher than a specific cut off point, Addison's disease is highly unlikely and other diseases can be considered as causes of the patient's problems. If the result is low, then Addison's disease is not ruled out and the full ACTH stimulation test should be performed. In certain circumstances, a screening test may prove useful rather than jumping to the more costly full ACTH stimulation test; however, if the goal is saving money it is important to realize that one may end up having to follow the screening test with the definitive test depending on the results.

Treatment

The most important aspect of treatment for hypoadrenocorticism is replacing the missing mineralocorticoids hormones. One way to do this is with oral fludrocortisone (Florinef®). Florinef is given usually twice a day at a dose determined by the patient's sodium and potassium blood tests. At first, these electrolytes are monitored weekly. When levels seem stable, these blood tests are repeated two to four times per year. Often with time, it will be found that the Florinef dose needed will increase. This increase is unfortunate as the medication is relatively expensive. Since Florinef has glucocorticoid activity as well as mineralocorticoid activity, it is usually not necessary to use additional medications for treatment. Using a compounding pharmacy may be helpful in managing the costs of this particular medication, especially in a larger dog.

Another way to treat this condition is with an injectable medication called DOCP (brand names Percorten-V or Zycotral®). This treatment is given approximately every 25 days. Electrolytes are measured prior to injections at first but testing can usually eventually be tapered to once or twice a year. There is some feeling among experts that DOCP produces better regulation of electrolytes than does oral Florinef. Dogs on DOCP, however, do require glucocorticoid supplementation (such as a low dose of prednisone).

What is Atypical Addison's Disease?

Most dogs become Addisonian when they lose the ability to produce both mineralocorticoids and glucocorticoids. They need both types of hormones replaced. It turns out that there is a subset of Addisonian dogs that are able to control their sodium/potassium imbalance through other hormones and only the glucocorticoids need to be supplemented. These patients have what is called atypical Addison's disease. They can have all of the symptoms of typical Addison's as described above (chronic relapsing diarrhea/appetite loss, low blood sugar crisis etc.) but not the electrolyte shock crisis. Treatment is supplementing with glucocorticoid hormones, such as prednisone.

It was previously thought that these patients experienced only partial damage to their adrenal cortex and that is why they did not suffer full Addison's symptoms. More recently, however, it has been discovered that atypical Addison's patients do have as much adrenal cortex damage as the typical ones; they are just finding other ways to manage their sodium and potassium. Most atypical Addison's patients progress to the typical form, which means they will eventually need more aggressive treatment with Florinef® tablets or Percorten® injections. The current recommendation is to monitor sodium and potassium levels every couple of months in atypical patients to watch for the switch to the typical (and more serious) form of Addison's disease.

What is Secondary Addison's Disease?

CTH is the hormone made by the pituitary gland in times when glucocorticoid hormones are needed. The pituitary gland feels the deficiency and sends a message to the adrenal gland telling it to produce and release more glucocorticoids. If the patient is being given glucocorticoids as a medical treatment, the pituitary will perceive that there are plenty of glucocorticoids in the body and will not release ACTH. The inner layers of adrenal cortex where glucocorticoids are made will atrophy. If medication is abruptly discontinued after long-term use, the adrenal glands will be too atrophied to cover the body's demand for glucocorticoids. This creates a deficiency in glucocorticoids similar to atypical Addison's disease and is the reason why steroid hormones are typically tapered off rather than abruptly discontinued.

True atypical Addison's disease can be distinguished from overuse of medication by a plasma ACTH level (high in atypical Addison's disease and low with medication overuse). This is not simply of academic interest. The patient with secondary

Addison's disease is never going to progress to typical Addison's disease and does not require long-term periodic monitoring of electrolytes.

Extended corticosteroid use is not the only way to get secondary Addison's disease. Some dogs have pituitary glands that naturally secrete inadequate ACTH. ACTH is the hormone that tells the adrenal gland to produce and release its glucocorticoids. The pituitary may be diseased and unable to produce ACTH. When a patient appears to have the atypical form of Addison's disease, an ACTH level may be recommended to distinguish atypical from secondary Addison's disease.

What is Pacific Rimism?

Dog breeds originating in the Pacific Rim, such as the Akita and Shiba inu, commonly have elevated potassium levels on blood tests. This can be confusing when a patient has symptoms that suggest Addison's. These patients will have normal ACTH stimulation test results if they do not have Addison's disease.

Whipworm Infection?

Whipworm infection has been known to create a syndrome nearly identical to Addisonian crisis, complete with abnormal sodium and potassium values. These patients will have normal ACTH stimulation tests but because whipworms only periodically shed eggs, fecal testing may not detect whipworm infection. If there is any question about whipworm infection, treatment should be instituted.