An Addisons Update

Written by: Linda Aronson, DVM

The Basics: Hypoadrenocorticism – the correct term for Addison's – is caused by the adrenal glands, situated near the kidneys, failing to secrete enough glucocorticoid (primarily cortisol) and mineralocorticoid (primarily aldosterone) hormones. In the majority of cases both types of hormone are affected. Less commonly the problem is not with the adrenal glands but with the pituitary gland. The pituitary secretes a hormone called adrenocorticotrophic hormone (ACTH), which regulates the adrenal secretion of cortisol and has little effect on aldosterone. In these cases of secondary Addison's only glucocorticoid secretion is generally affected. The secretion of aldosterone is regulated by a number of factors, but the most important is the level of potassium ions in the serum.

By far the most common cause of primary adrenal failure is autoimmune disease, but it can be the result of granulomatous disease, hemorrhage, inflammation, infarction (due to interrupted blood supply), cancer or the deposition of amyloid tissue in the adrenal glands. Immune mediated destruction of the adrenal glands often occurs in conjunction with other autoimmune endocrine diseases such as thyroiditis (hypothyroidism), diabetes mellitus or hypoparathyroidism. Lesions of the hypothalamus or pituitary can result from a tumor or other space occupying lesion.

Drugs given to treat hyperadrenocorticism (Cushing's disease) – mitotane, trilostane or ketoconazole – can result in Addison's due to adrenal destruction/suppression, in the case of mitotane this is not reversible, but adrenal function will usually rebound once the patient stops taking the other two drugs. Ketoconazole is also given to treat fungal infections. Corticosteroids, such as prednisone, suppress an animal's normal adrenal production and release of glucocorticoids, as well as causing adrenal atrophy. This can happen within a few days, and abrupt termination of these drugs can result in symptoms of Addison's, and is by far the most common cause of secondary Addison's disease. The biggest risk is from the long acting glucocorticoid drugs, which can suppress adrenal function for five to six weeks.

Diagnosing Addison's is complicated by the wide range of presenting symptoms. In some dogs there will be acute collapse, while in others symptoms come on gradually and may wax and wane, so that the owner is

not really aware how sick the dog was until treatment shows a significant improvement. 85 or 90% of adrenal hormone reserves have to have been depleted before a dog will show clinical signs, and usually some stress then triggers the onset of illness. Lack of glucocorticoids can produce loss of appetite, vomiting, lethargy/depression, weakness, weight loss, diarrhea, blood in the stool (melena), shivering, increased urination and drinking, as well as abdominal pain. Not all dogs will show all these symptoms. When the mineralocorticoids are also affected signs tend to be more severe with dehydration, shock and collapse accompanying the other signs. Gastrointestinal hemorrhage and seizures (due to low blood sugar and electrolyte imbalances) are less common signs. Heart rate slows, and pulses become weak, in some cases the heart may stop beating and death may be the first symptom.

Blood work can be equally confusing. The hematocrit can be increased by dehydration or show anemia. In about 20-30% of cases white cell counts will be elevated, especially eosinophil and lymphocyte numbers, a so called stress leukogram, due to decreased glucocorticoids. If aldosterone is deficient there will be significant electrolyte abnormalities with reduced sodium and chlorine and increased potassium, calcium and phosphate. The role of aldosterone is to increase retention of sodium and water by the kidneys. Without it, urine is dilute and the animal easily dehydrated. Lack of aldosterone also results in hydrogen ion retention and a mild acidosis. Albumin (protein), cholesterol and glucose levels tend to be low, while liver enzymes may be elevated.

One study showed that 24% of dogs diagnosed with Addison's did not have classic electrolyte abnormalities, and the percentage may be higher in some breeds. These atypical cases may be due to secondary Addison's – affecting only the pituitary or hypothalamus – or occur because the areas of the adrenal glands producing glucocorticoids only or primarily have been affected. While some cases of atypical Addison's go on to include diminished mineralocorticoid production, by no means all of them will. Dogs with atypical Addison's tend to be older, have had a longer duration of symptoms prior to diagnosis, and be low in protein and cholesterol.

A sodium:potassium ratio of less than 27 or 28 is strongly indicative of Addison's disease, but it is only useful in dogs with mineralocorticoid involvement. In these cases it is a powerful diagnostic tool, but not absolutely accurate (~95%). Care should be taken particularly in cases in

which one electrolyte is significantly affected (high potassium, low sodium) while the other is well within the normal range or even high normal for sodium). In cases of atypical Addison's the sodium:potassium ratio is generally completely normal, and levels of sodium and potassium well with reference ranges.

Imaging is of little value. In typical Addison's you will generally see a smaller than normal heart and liver and narrowing of cardiac blood vessels. The adrenal glands may also appear small, but this is subjective. Elevated potassium will produce characteristic changes in the EKG, but are not diagnostic. A basal cortisol of <2 micrograms/dl is 100% predictive of Addison's but not diagnostic.

Diagnosis. To diagnose Addison's you need an ACTH stimulation test. In this test the dog's basal serum cortisol is measured. He is then injected with a dose of synthetic ACTH and the level of cortisol is recorded again an hour later. (One dose of dexamethasone can have been administered prior to the test if necessary to treat a dog in crisis.) In dogs with Addison's (typical or atypical) pre and post cortisol levels are usually less than 1 mcg/dl, but should definitely be below the lab's reference range. This range can vary depending upon the laboratory doing the testing, but is usually <5mcg/dl. Inadequate response will also be seen in dogs that have been treated for Cushing's or with glucocorticoids. Some dogs with sex-hormone secreting adrenal tumors may also fail to respond. The ACTH hormone is not terrifically stable, and loss of activity of the ACTH used may lead to a false diagnosis. A borderline post ACTH level of cortisol should be retested in four to eight weeks to see if the dog was in the early stages of adrenal failure.

In cases of atypical Addison's, measuring serum ACTH can determine whether the disease is adrenal (primary, normal ACTH levels) or secondary (pituitary, subnormal levels). The former are more likely to progress to full-blown Addison's disease, and electrolyte levels should be tested at regular intervals. In one study of 11 dogs with atypical Addison's, only one developed mineralocorticoid deficiency although 9 of the 11 had primary (adrenal) disease, however. Measuring plasma aldosterone does not appear to be helpful in reaching a diagnosis or distinguishing different types of Addison's disease.

Treating Atypical Addison's disease: Conservatively between 5 and 10% of dogs with primary hypoadrenocorticism only have a glucocorticoid deficiency. Symptoms tend to be relatively mild and in most cases look like a gastrointestinal upset with weight loss, vomiting, loss of appetite, and – especially in small lean dogs – low blood sugar. The ACTH stimulation test should be run in any dog with vague waxing and waning clinical signs, general malaise and weight loss. If the ACTH stimulation test result is consistent with Addison's but sodium and potassium levels are normal – atypical Addison's – glucocorticoid supplementation should be given as 0.2 to 0.4 mg/kg prednisolone a day, and electrolyte levels and general health should be monitored every three to four months for a year. If sodium or potassium concentrations or both become abnormal the disease has probably progressed to typical Addison's. Some veterinarians advocate measuring serum aldosterone concentrations pre and post ACTH stimulation for confirmation, but this test is not yet widely available, and has not proven particularly accurate. Atypical Addisonians should not receive mineralocorticoids.

Treating an Addisonian Crisis: During an Addisonian crisis time is of the essence. If Addison's disease is suspected in a previously undiagnosed dog in extremis, blood and urine samples should be collected for a complete blood count, serum biochemistry, serum cortisol and urinalysis prior to any treatment. The dog is then given synthetic ACTH for the ACTH stimulation test, and blood collected an hour later for cortisol evaluation. (If synthetic ACTH is not available it is more important to stabilize the dog, and run this test later.) During the hour, shock doses of 0.9% sodium chloride (fluids) are given to resolve the loss of blood volume and blood pressure. The glucocorticoid dexamethasone is given intravenously (as it doesn't affect the ACTH stim test result as oral prednisone or prednisolone would). The dog should be kept warm to prevent or resolve hypothermia. Mineralocorticoids are also given. It is preferable to give desoxycorticosterone pivalate (DOCP, Percorten V) intramuscularly. Even given daily Percorten does not produce adverse effects in healthy dogs, and so it can safely be given in suspected cases of Addisonian crisis even if this proves not to be the problem. (Giving the drug subcutaneously is contraindicated in dehydrated dogs, which dogs in Addisonian crisis typically are, due to poor absorption.) Florine-f – fludrocortisone acetate – may be substituted if Percorten is not available. It has both mineralocorticoid and glucocorticoid activity, but has to be given orally and dogs in Addisonian crisis usually have significant gastrointestinal upset – vomiting, gastric bleeding – limiting assimilation. Percorten also

corrects electrolyte abnormalities better than Florine-f. After one or two hours replacement fluids are reduced to maintenance levels. If the dog has not responded well within 24 hours, the diagnosis should be reevaluated.

Maintenance therapy: Electrolyte levels of dogs treated with DOCP should be checked 2 weeks after the initial dose, and then at weekly intervals. This is necessary to determine the appropriate dose between DOCP injections. Once either potassium rises above laboratory normals of sodium drops below the laboratory reference range, or both, it is time for the next shot. This interval can range from every two to every 8 weeks. Novartis, the manufacturer of Percorten, recommends an initial dose of 1mg/lb body weight, but I find most dogs of Beardie size or larger do well with an initial dose of 0.5 mg/lb. If electrolyte levels are still normal after four weeks an even smaller dose can be given the next time.

Maintenance doses can be given either subcutaneously or intramuscularly, so owners should be able to give the shots themselves to lower their costs once the dog is stabilized. While Florine-f can be used for maintenance treatment, it does not stabilize sodium and potassium concentrations as effectively as Percorten and is more expensive for dogs weighing more than 25 lbs. With stable dogs it is only necessary to recheck electrolytes every four to six months or if the dog becomes ill. Because Percorten has no glucocorticoid activity it is necessary to give prednisolone (Beardies tolerate the artificial drug better than prednisone) at a dose of 2.5 or 5 mg every day or every other day. The dose must be increased if the dog is stressed or if a stressful situation is anticipated. In this case increase the prednisolone dose two or three days before the anticipated stress – travel, visitors, hospitalization, etc.

While Addison's is not a disease anyone would wish for, most dogs are well maintained and can expect a fairly normal life span and other diseases are usually responsible for their deaths. Owners become especially keyed into their dogs and recognize situations that cause their dog stress and tweak drug doses accordingly. One of the biggest risks now seems to be that anytime the dog appears not to be functioning optimally owners increase medication dose, often without consulting their veterinarian. This response seems to be encouraged by the Internet Addison's groups. As a result I have seen a lot of dogs over-medicated several fold. If your dog is taking more than the recommended dose of either Percorten or Florine-f (0.015-0.2 mg/kg/day, although I have maintained Addisonian Beardies well on doses

as low as 0.1 mg a day), do consider the possibility that your dog is being over-medicated. Fortunately, there is less risk of this happening if the dog is getting Percorten injections.