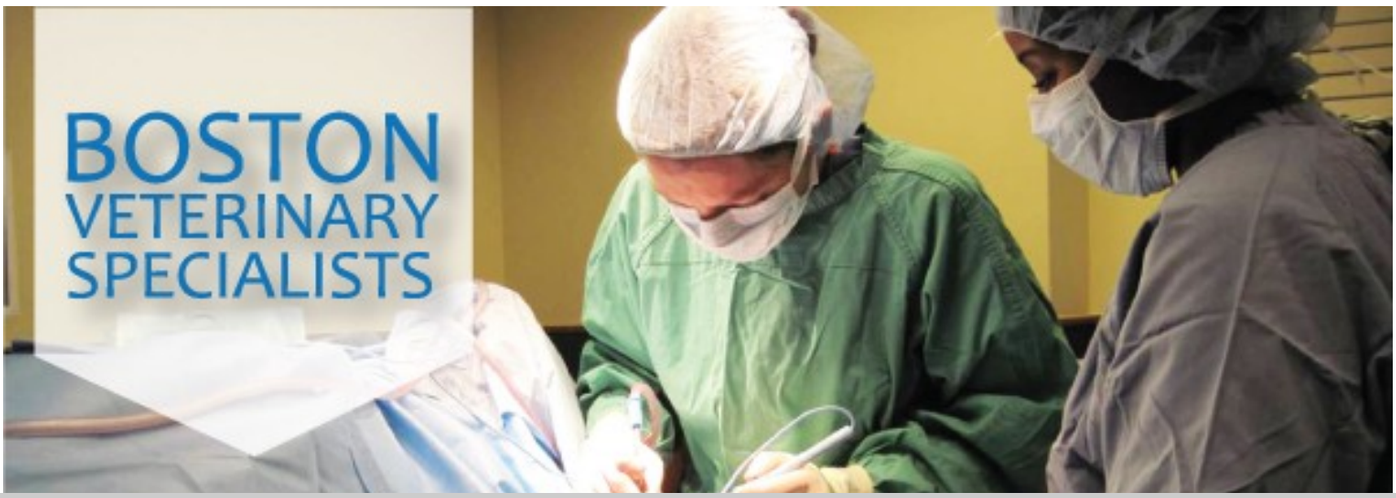

Monthly Update **April 2013**
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Editor: William B. Henry DVM, DACVS

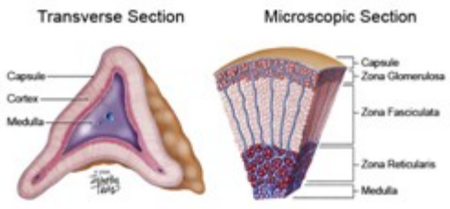
Endocrine Emergencies Part 1: Addison's Disease

Editor's Note: Endocrine Emergencies will be a two part newsletter. Part 1: April will cover Addison's Disease. Part 2: May will cover Diabetic-ketoacidosis (DKA) and Thyrotoxicosis aka "Thyroid Storm".

This is a review of three endocrine emergencies that are common in an emergency room setting: hypoadrenocorticism, diabetic ketoacidosis and thyrotoxicosis. For each disease, there will be a brief overview of the disease pathogenesis, common clinical signs, followed by diagnosis, treatment and overall prognosis.

Hypoadrenocorticism:
Hypoadrenocorticism, also known as Addison's disease, is defined as the deficient production of glucocorticoids and/or mineralocorticoids by the adrenal cortex. Understanding the anatomy of the adrenal glands is important for understanding the pathophysiology of Addison's disease, as each of these adrenocortical hormones has vastly different functions as well as different stimulants leading to their production.

Anatomy
The adrenal gland is divided into the cortex and the medulla. The cortex is made up of three layers. The outer layer, the zona glomerulosa, where mineralocorticoids (aldosterone) are produced. The middle layer, the zona fasciculata, is where glucocorticoids (cortisol) are produced, and the innermost layer, the zona reticularis, is where sex hormones (and some cortisol) are produced. The adrenal medulla, which is not involved in Addison's disease, is where catecholamines (epinephrine, norepinephrine) are produced.



The main job of aldosterone is electrolyte and total body water homeostasis. By promoting sodium reabsorption, aldosterone leads to secondary water retention and an increased effective circulating volume. In this way, aldosterone helps protect against hypotension by maintaining normovolemia. Aldosterone also acts to protect the body from hyperkalemia by enhancing potassium excretion. Lack of aldosterone leads to hyperkalemia, hyponatremia and hypovolemia.

The primary stimulus for aldosterone secretion is the renin-angiotensin-aldosterone system (RAAS). Renin is released from the juxtaglomerular apparatus in the kidney in response to hypotension, reduced renal blood flow, sodium and chloride receptors in the macula densa, as well as secondary to sympathetic stimulation. Renin facilitates the conversion of angiotensinogen to angiotensin I, which then gets converted to angiotensin II via angiotensin-converting enzyme in the lungs and other tissues. Angiotensin II stimulates the zona glomerulosa

Continued next page

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CCVS:
Dr. Louisa Rahilly:
May 21, 2013, *"Steroids in veterinary medicine: Friend or Foe."*

Dr. Daniel Beaver:
June 4, 2013, *"Hip Dysplasia"*

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cells to secrete aldosterone, which then stimulates cells in the kidneys to reabsorb sodium and excrete potassium. The next most powerful cause for aldosterone secretion is hyperkalemia, which directly stimulates the cells in the zona glomerulosa to release aldosterone. The final stimulus for aldosterone secretion is adrenocorticotropic hormone (ACTH), which is released from the hypothalamus, however it plays a more minor role in sodium regulation.

Loss of the following glucocorticoid functions in Addison's disease results in the main symptomatology of the Addisonian crisis: gluconeogenesis and response to stress (via the proper production of catecholamines and adrenergic receptor function). It is important to remember, however that glucocorticoids have numerous other functions, such as regulating carbohydrate, lipid and protein metabolism, modulation of the immune system, and stabilizing cell membranes. A full description of glucocorticoid function can be found in Guyton and Hall, Medical Physiology Text, 11th edition, chapter 77. A lack of glucocorticoids in Addison's disease leads to decreased gluconeogenesis and glycogenolysis resulting in hypoglycemia and decreased vascular sensitivity to catecholamines and subsequent hypotension.

Cortisol is almost entirely regulated by the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus secretes corticotropin -releasing hormone (CRH). This stimulates the pituitary gland to produce ACTH, which directly stimulates the zona fasciculate to release cortisol. Cortisol then travels via the bloodstream to the hypothalamus and pituitary gland and inhibits both CRH and ACTH release to prevent cortisol levels from continuing elevate after the initial rise in cortisol concentration.

Primary Hypoadrenocorticism

Hypoadrenocorticism can be divided into primary (classic Addison's disease) or secondary hypoadrenocorticism. Primary hypoadrenocorticism is typically due to destruction of a large portion (greater than or equal to 90% destruction) of both adrenal cortices, which leads to a deficiency of ALL adrenocortical hormones resulting in these patients being deficient in both aldosterone and glucocorticoids. This is commonly an immune-mediate destruction in dogs; however, other causes include iatrogenic destruction (i.e. via treatment of hyperadrenocorticism with Mitotane or Vetoryl), hemorrhage, infarction, infiltrative disease, or trauma to the adrenal glands, as well as the use of certain drugs (i.e. megesterol, etomidate and ketoconazole), which can impair adrenal gland hormone production.

Secondary Hypoadrenocorticism

Secondary Hypoadrenocortisism is characterized by decreased secretion of ACTH from the anterior pituitary gland, leading to impaired secretion of glucocorticoids from the adrenal cortex. Mineralocorticoid production is typically normal in these patients because ACTH has only a minor effect on mineralocorticoid secretion. Secondary hypoadrenocorticism is typically iatrogenic, secondary to suppression of ACTH by drug therapy with exogenous glucocorticoids or progesterones, but it can also be secondary to tumors, trauma or even congenital pituitary defects leading to decreased ACTH production. This is less commonly associated with an emergent Addisonian crisis, since their mineralocorticoid function (and therefore sodium/water balance) should be adequate, but it is possible.

Risk factors

Addison's disease typically affects young to middle aged dogs. The average age is 4 years, but the range is very wide, with animals as young as 2 months or as old as 14 years being reported with this disease. It does tend to affect females more than males, and intact females have a significantly higher risk of developing Addison's than spayed females. Many breeds of dogs can get this disease but some have a greater risk, such as Great Danes, Portuguese Water Dogs, Rottweilers, Standard Poodles, West Highland White Terriers, Soft Coated Wheaten Terriers, Bearded Collies, Leonbergers, and Nova Scotia Duck Tolling Retrievers.

Clinical signs



Suspicion for Addison's disease can begin with a history and a physical exam. Historical findings may include a waxing/waning history of chronic, intermittent GI signs, weight loss and lethargy, with clinical signs sometimes worsening with stress. Alternatively, these patients may have never been sick before. The major physical exam findings will often be secondary to hypovolemic shock (Addisonian Crisis), as these animals have lost the ability to maintain normovolemia due to lack of sodium reabsorption. These patients are often weak, collapsed or recumbent, with poor pulse quality and oftentimes have a depressed or obtunded mentation. One of the standout physical exam findings is a relative bradycardia. Their heart rates are often below what you'd expect for a patient in shock. This is secondary to the hyperkalemia, which is due to lack of mineralocorticoids. Other common clinical signs will be diffuse vomiting, diarrhea, abdominal pain, dehydration and sometimes hypothermia.

Diagnosis

The ACTH stimulation test is the diagnostic gold standard for confirming the presence of Addison's disease. There are some abnormalities on routine blood work, however, which may help provide an index of suspicion. Electrolyte abnormalities consisting of hyponatremia and hyperkalemia secondary to mineralocorticoid deficiency, with a sodium: potassium ratio < or = 27 are very suggestive for Addison's disease. This abnormal ratio does not provide a diagnosis, however, as other disease processes may also result in a similar Na: K ratio, such as chronic or acute renal failure, third spacing of fluids (i.e.: pericardial, pleural or abdominal effusions), massive GI fluid loss/parasitism (i.e.: whipworms), or even late term pregnancy. Be sure to image the chest/abdomen with radiographs or ultrasound in these patients to look for signs of free fluid.

In addition, if the patient is glucocorticoid deficient with normal mineralocorticoids (i.e.: secondary hypoadrenocorticism) these patients may present with completely normal electrolytes. Secondary hypoadrenocorticism is a less common cause of an Addisonian crisis, however glucocorticoid deficiency can lead to gastroenterocolitis, which, if severe enough, could lead to hypovolemic shock and crisis.

Addisonian patients will often have an "abnormally normal" CBC without the expected stress response seen in patients with shock, characterized by lymphopenia and eosinopenia. This is due to lack of cortisol, which is the underlying hormone responsible for the stress response. The Addison's patient reminds the astute clinician that it is valuable to look at every CBC critically. Glancing at only the abnormal values could make one miss the absence of "typical" abnormalities such as a stress leukogram. A normal lymphocyte count and a high -normal or elevated eosinophil count in a patient who is undergoing a physiologic stress is abnormal. There may also be a normocytic-normochromic non-regenerative anemia, however this may initially be masked by dehydration.

The biochemistry panel may reveal abnormalities that are directly related to hypovolemia and dehydration. Azotemia is very common, typically due to reduced renal perfusion, though the increased BUN can be from GI bleeding as well. Hyperphosphatemia can be present as part of the pre-renal syndrome. Hypoalbuminemia may be secondary to GI loss, impaired GI absorption or even impaired synthesis. Liver enzyme elevation may be seen, likely secondary to decreased cardiac output and poor tissue perfusion. Hypoglycemia may be seen secondary to glucocorticoid insufficiency.

Imaging these patients may reveal non-specific signs of hypovolemia on thoracic radiographs such as microcardia, decreased pulmonary vessels size, reduced size of the caudal vena cava and possibly microhepatica. Less commonly, mega esophagus may be seen. This is suspected to be secondary to generalized muscle weakness, however this typically resolves with treatment. Abdominal ultrasound may reveal bilateral adrenocortical atrophy.

As noted above, an ACTH stimulation test is the gold standard for diagnosing Addison's disease. This requires a baseline cortisol prior to administering a synthetic ACTH analog (Cosyntropin or ACTH gel) and a 1 hour post stimulation cortisol level. Pre- and post-stimulation cortisol values that remain < 2 µg/dL are diagnostic for Addison's. A 2007 JAVMA paper evaluated the use of basal cortisol concentration as a screening tool for hypoadrenocorticism. They found that 80% dogs with basal cortisol concentrations >2 µg/dL were very unlikely to have Addison's disease while NO dog with Addison's had baseline cortisol of >2 µg/dL Thus, these data support the use of a baseline cortisol level as a screening tool for Addison's. If the baseline value comes back as >2 µg/dL, the patient likely does not have Addison's, however, if the baseline cortisol comes back as <2 µg/dL, the entire stimulation test should be completed to confirm or deny the presence of Addison's. This screening test is most helpful in the stable patient. If the patient in question is in shock, a full ACTH stimulation test should be performed as rapidly as possible so that steroids may be given.

Treatment

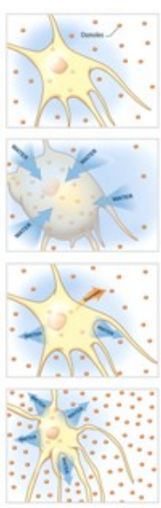
The primary goals in treating an Addisonian crisis are IV volume resuscitation, correcting electrolyte abnormalities, providing glucocorticoids and mineralocorticoids, as well as recognizing and correcting life-threatening cardiac arrhythmias.

Fluids and Sodium

The main manifestation of this disease is life-threatening hypovolemic shock, so fluid therapy is the most important initial treatment for patients in a suspected Addisonian crisis. During the initial resuscitation phase, rapid boluses of fluids are administered until the patient's physical exam parameters, blood pressure and lactate measurements have normalized and indicate a return of adequate perfusion and cardiovascular stability. The commonly quoted shock dose is 90ml/kg in dogs and 45ml/kg in cats, however these are simply guidelines based on the average blood volume of these species. Continue resuscitation with IV fluid boluses until the aforementioned parameters have normalized and the patient shows signs of cardiovascular stability and improving mentation.

During the resuscitation period, fluid choice is of utmost importance to avoid altering plasma sodium concentration too rapidly. Attempts should be made to match the sodium concentration of the patient with that of the resuscitation crystalloid. Normal 0.9% NaCl has historically been recommended as the fluid of choice for initial volume replacement in dogs in an Addisonian crisis. The concern, however, when administering large volumes of 0.9% NaCl is the potential for the acute rise in serum sodium as well as the acidifying effects on the body. Bolusing such a sodium-rich fluid can result in central pontine myelinolysis (cerebral dehydration), also known as Osmotic Demyelination Syndrome. A 2003 case report from Ontario Veterinary College described an 18-month dog who exhibited neurologic signs after his serum sodium increased by 38 mmol within 48 hours during treatment for Addison's. He required intensive care during this crisis, but did make a full recovery.

Osmotic Demyelination Syndrome



Organic osmolytes are present within the cells of our brains, which function as tonicity buffers, to avoid rapid fluid shifts into and out of neural cells secondary to changes in plasma tonicity. Osmolytes equilibrate with the surrounding extra-cellular osmolality over the course of 2-3 days to avoid these rapid fluid shifts. With Addisonian patients, who have typically been hyponatremic for days, their cells have already equilibrated with the surrounding, extracellular hypotonic environment by getting rid of their organic osmoles to become hypotonic intracellularly. If rapid fluid resuscitation occurs, and their sodium is replaced faster than they can remake or regain their lost osmoles, the extracellular fluid becomes more hypertonic compared to the intra-cellular compartment, which leads to rapid equilibrating and movement of water out of the cells. This results in brain dehydration and injury, which we call osmotic demyelination syndrome (or central pontine myelinolysis). The associated lesions in the brain typically take several days to develop, so this will not be clinically manifested immediately. Clinical signs can range from lethargy and weakness to ataxia, progressing to hypermetria, quadriparesis, and other postural deficits.

The target sodium correction rate should be less than 10 to 12 mEq/L/day (0.5 mEq/L/hr). The actual rate of correction may not correspond to the calculated rate of correction, so serial monitoring of electrolytes is essential to ensure no major sodium shifts occur.

Once the patient has been resuscitated, they will need to be on IV fluids until they are rehydrated, have normalization of renal azotemia (if no underlying renal disease is suspected), normalized electrolytes and they are eating and drinking on their own. Higher fluid needs should be expected of aldosterone, as well as increased losses from any vomiting and diarrhea. These patients often need 120-180mL/Kg/day (6-8mL/kg/h), although exact fluids prescriptions are best made by the attending clinician.

Hyperkalemia

A major electrolyte abnormality that needs to be addressed in these patients is hyperkalemia. The initial fluid diuresis is typically sufficient in treating hyperkalemia, however, if the patient's hyperkalemia is sufficient enough to result in a severe bradycardia with classic ECG abnormalities (reduced to absent P waves, increased QRS duration, tall, tented T wave) then more aggressive treatment is needed.

Calcium gluconate (dose: 0.5-1.5mls/kg, given IV over 2-5 minutes while monitoring the ECG) is used to help stabilize the cardiac membrane by restoring the normal difference between the cardiac resting and threshold potentials. It does not result in any changes in plasma potassium concentration.

To improve potassium concentration, regular insulin (dose: 0.25u/kg IV) and/or Dextrose (dose: 0.5-1ml/kg 50% Dextrose, diluted 1:1, followed by 5% Dextrose CRI) can be given to drive potassium into the cells. These need to be followed up with regular (q 2-3 hours) blood glucose monitoring to ensure patients don't develop severe hypoglycemia subsequently.

Initial Hormone Replacement

Treatment with glucocorticoids needs to be started early in course of disease. If an ACTH stimulation test hasn't been performed, Dexamethasone SP (dose: 0.1-0.2mg/kg IV q12) should be used, as this steroid doesn't interfere with the cortisol assay of the ACTH stimulation test. This drug and dose should be continued until the patient can go on oral prednisone. Avoid the use of other steroids (i.e.: Hydrocortisone sodium succinate, Prednisolone sodium succinate, etc.) prior to obtaining samples for the ACTH stimulation test as these all interfere with the cortisol assay and can result in ACTH stimulation results not supportive of Addison's when the disease is actually present (false negative).

It is not essential in the emergent treatment of an Addisonian crisis to administer exogenous mineralocorticoids (Percortin/ DOCP or Florinef/Fludrocortisone). Due to potential side effects (fluid overload, hypokalemia), these medications are only started once the ACTH stimulation results give a diagnosis of Addison's. Other general supportive care measures often required are: treatment of hypoglycemia, administering GI protectants and opioid analgesic medications on an as needed case-by-case basis. Remember that non-steroidal anti-inflammatory medications should NEVER be administered with supra-physiologic doses of glucocorticoids and thus are contraindicated in the treatment of the acute Addisonian crisis.

Prognosis:

If the patient survives the initial crisis, their long-term prognosis is very good to excellent with life-long therapy. The median survival time is reportedly 5 years, but each patient should have a normal life expectancy as long as the owners continue life-long treatment with a synthetic aldosterone analogue and steroid equivalent.

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Tech Tip

Editor's Note: We have used cold compress therapy during the first 24 hours post-op for the past several years on all our orthopedic surgery cases. Our surgery technicians use hand compression rather than pneumatic compression as was used in this study. We feel it helps minimize post-op pain. This paper was given at the ACVS Symposium in 2012 substantiated our subjective assumption.

Prospective Evaluation of Cold Compression Therapy On Postoperative Pain, Swelling, Range of Motion and Lameness Following Tibial Plateau Leveling Osteotomy

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Introduction: Cold compression therapy (CCT), the use of cold therapy combined with intermittent pneumatic compression, is currently used in human medicine to treat postoperative pain, decrease swelling and improve limb function following knee surgery. Our objective was to determine the effect of CCT on postoperative pain, swelling, range of motion and lameness in dogs undergoing tibial plateau leveling osteotomy (TPLO).

Materials and Methods: Thirty-four dogs undergoing TPLO were included in the study and randomly assigned to one of two groups. Group 1 received CCT during the 24 hour postoperative period and group 2 received no CCT. Pain, degree of lameness, stifle range of motion and swelling were evaluated preoperatively, 24 hours, 14 days and 28 days postoperatively. Logistic regression and linear regression analysis were used to compare the measured variables. $P < 0.05$ was considered significant.

Results: Treatment resulted in significantly lower pain scores ($p=0.004$), decreased lameness ($p=0.001$), increased range of motion ($p=0.003$) and decreased stifle swelling ($p=0.008$) 24 hours postoperatively. No difference in the outcome measures were observed at 14 and 28 days postoperatively.

Discussion/Conclusion: Our study supports the use of CCT as part of a multimodal approach to decrease pain and swelling and improve limb function in the immediate 24 hours following TPLO. The benefits of CCT reported here are likely related to the decrease in pain and inflammation and improved regional tissue perfusion achieved during the treatment period.

Acknowledgments: Cold compression units were provided by Game ReadyEquine, Coolsystems Inc.