Hypoadrenocorticism (Addison’s disease) is a syndrome resulting from glucocorticoid and mineralocorticoid deficiency. In most cases of hypoadrenocorticism the abnormality is located in the adrenal cortex (primary adrenal failure), resulting in deficiency of usually both cortisol and aldosterone from the adrenal cortex. More rarely, Addison’s disease may be due to dysfunction of the hypothalamic-pituitary axis resulting in a failure of ACTH secretion and pure glucocorticoid deficiency (secondary adrenal failure). In secondary hypoadrenocorticism, mineralocorticoid secretion is normal.

ADRENAL PHYSIOLOGY

Glucocorticoids: Glucocorticoids are synthesized by the zona fasciculata and reticularis in the adrenal cortex. They stimulate gluconeogenesis and glycogenesis, and enhance protein/fat catabolism. Glucocorticoids are important in maintaining normal blood pressure and counteracting the effects of stress.

Mineralocorticoids: Mineralocorticoids are synthesized from the zona glomerulosa of the adrenal cortex. They promote sodium, chloride and water reabsorption and potassium excretion (site of action proximal & distal convoluted tubules). Release of mineralocorticoids is regulated by the renin-angiotensin system, the plasma potassium concentration and to a lesser extent, the ACTH concentration.

ETIOLOGY HYPOADRENOCORTICISM

Primary Adrenal Failure: Since most cases of hypoadrenocorticism are successfully treated, the underlying cause of adrenal destruction is usually not known in individual patients. In necropsy studies, immune mediated destruction is the most frequent histopathologic lesion identified. Adrenal destruction by granulomatous disease processes such as histoplasmosis, and blastomycosis has also been reported. Other causes of adrenal destruction include hemorrhagic infarction, adenalfat, neoplasia, amyloidosis and necrosis. Immune mediated destruction of the adrenal gland may also occur together with other immune mediated endocrine disorders such as hypothyroidism, diabetes mellitus, and hypoparathyroidism.

Secondary Adrenal Failure: Destructive lesions in the hypothalamus or pituitary due to neoplasia, inflammation, or trauma may cause secondary hypoadrenocorticism. Idiopathic ACTH deficiency may also occur.

Iatrogenic: Primary adrenal failure may be caused by a number of drugs including mitotane and ketoconazole. Adrenal suppression caused by ketoconazole is reversible but adrenal failure caused by mitotane is often permanent. Administration of glucocorticoid drugs may cause secondary adrenal failure. After corticosteroid administration (topical, oral, or injectable) suppression of ACTH production from the pituitary gland occurs within a few days. This results in secondary adrenal atrophy. How long the adrenal axis is suppressed depends on the potency and half-life of the administered glucocorticoid. Long acting depot drugs are the most potent suppressants and can cause suppression for 5 - 6 weeks or longer.

CLINICAL SIGNS

Signalment: Seventy percent of cases are female, and most are young to middle-aged dogs (mean 4 - 5 years). Mixed breed dogs are most commonly affected. The disease is suspected to be heritable in the Standard Poodle, Leonberger, and Nova Scotia duck tolling retriever.

History: Clinical signs may be either acute or gradual in onset and often wax and wane. Owners may not realize how long the dog has been ill until treatment results in a dramatic improvement in activity level. Since 90 percent of adrenal reserve must be depleted before clinical signs are observed, it may require a stressful event to trigger clinical illness. Clinical signs may be very vague and are rarely pathognomonic for the disease. Anorexia, vomiting, lethargy/depression, weakness, weight loss, diarrhea, shaking/shivering, polyuria, polydipsia, and abdominal pain may be observed. Clinical signs such as weakness, lethargy, weight loss, can occur due to glucocorticoid deficiency alone. If mineralocorticoids are deficient, the clinical signs tend to be more severe and polyuria, polydipsia, hypovolemic shock, collapse and dehydration are often present. Less common clinical signs include acute gastrointestinal hemorrhage, and seizures due to hypoglycemia or electrolyte derangement.

Physical examination: The physical examination may be normal or may reveal lethargy, weakness, dehydration, bradycardia, weak pulses, decreased capillary refill time, and other evidence of hypovolemic shock.

DIAGNOSTIC TESTING

Clinical Pathology: Complete blood count may reveal a normocytic normochromic anemia (nonregenerative), and eosinophilia, neutrophilia or lymphocytosis (inconsistent). The hematocrit may also be increased due to dehydration.
A chemistry profile may reveal hyponatremia, hypochloremia, hyperkalemia, hypercalcemia, and hyperphosphatemia. These changes occur due to aldosterone deficiency with a resultant failure of the kidneys to conserve sodium. This is accompanied by profound fluid loss, shift of K$^+$ ions to the extracellular compartment, pre-renal azotemia due to decreased renal perfusion and hypovolemia. A mild to moderate metabolic acidosis may also occur because a lack of aldosterone impairs renal tubular hydrogen ion secretion. Other serum biochemical abnormalities that are may occur in dogs with hypoadrenocorticism include hypoalbuminemia, hypcholesterolemia, hypoglycemia, and increased liver enzymes. Specific gravity of the urine is commonly less than 1.030 due to loss of the normal medullary concentration gradient and impaired water reabsorption by the renal collecting tubules. Thus it can be difficult to differentiate these dogs from those with primary renal failure.

The Na:K ratio is usually < 1:20 in hypoadrenocorticism and this is sometimes useful in emergency diagnosis and treatment. However, reliance on measurement electrolytes alone for diagnosis of hypoadrenocorticism can be misleading, because there are many other causes of these electrolyte changes (e.g. severe gastroenteritis). Conversely electrolyte concentrations and the Na:K ratio may be normal in both primary and secondary hypoadrenocorticism.

**Radiography:** Thoracic radiographs may reveal microcardia and a narrow posterior vena cava. The severity of the changes reflects degree of hypovolemia. Occasional dogs may have evidence of megaesophagus.

**Electrocardiogram:**
- Mild hyperkalemia (>5.5 meq/L) - peaked T wave, shortening of QT interval
- Moderate hyperkalemia (>6.5 meq/L) widened QRS complex
- Moderate - severe hyperkalemia (>7.0 meq/L) - decreased amplitude, increased duration P wave, P-R interval increases, P waves may disappear completely.
- Severe hyperkalemia (11 - 14 meq/L) ventricular fibrillation or asystole.

**Endocrine studies:**
An ACTH stimulation test is necessary to confirm the diagnosis of hypoadrenocorticism because not all dogs with hypoadrenocorticism have the expected electrolyte changes and because many other disorders may mimic the characteristic findings of Addison’s disease. It is acceptable to base emergency treatment upon electrolyte abnormalities, however an ACTH stimulation test should always be performed prior to initiating long term treatment. Measurement of a basal cortisol concentration is unreliable for diagnosis in most cases. For an ACTH stimulation test, synthetic ACTH (250 µg/dog or 5 µg/kg IV) may be used. In most cases of hypoadrenocorticism, both the pre and post ACTH cortisol concentration are less than 2 µg/dl. It is very important to use the protocol and reference range established by the laboratory being used. Other causes of a lack of response to ACTH include prior glucocorticoid administration (other than recent use of IV dexamethasone), lysodren or ketoconazole administration, use of inactive ACTH, and errors in administration of ACTH. Rarely dogs with sex hormone secreting adrenal tumors will have a flat line response to ACTH, however these dogs usually have overt signs of hyperadrenocorticism. In dogs with normal electrolytes, measurement of an endogenous (basal) ACTH concentration can also be useful in identifying the type of hypoadrenocorticism. Measurement of an increased ACTH concentration confirms a diagnosis of primary hypoadrenocorticism, while an ACTH concentration within or below the reference range is consistent with a diagnosis of secondary hypoadrenocorticism.

Rapid treatment of dogs with suspected Addison’s disease is vital especially if profound electrolyte abnormalities are present. Aims of treatment include:
(1) Correction hypotension/hypovolemia
(2) Correction electrolyte imbalance
(3) Provision immediate source glucocorticoid
(4) Correction acidosis, hypoglycemia, hypercalcemia

The following is the suggested procedure for dogs presenting with signs of hypovolemia in which Addison’s disease is suspected:
(1) Place IV catheter in cephalic or jugular vein
(2) Collect blood sample for measurement electrolytes, cortisol
(3) Synthetic ACTH administered IV, second cortisol sample 1 hour later.
(4) 0.9% saline IV, 30 - 80 ml/kg/24 hours started immediately. If shock is present use shock doses of fluid. In addition must correct for dehydration.
(5) Once the second blood sample is collected, administer prednisolone sodium succinate at a dose of 4-20 mg/kg IV, or hydrocortisone hemisuccinate or hydrocortisone phosphate at dose of 2-4 mg/kg IV or dexamethasone 0.5 to 2.0 mg/kg as an initial dose. Then add dexamethasone 0.05 - 0.1 mg/kg q 12 hours into fluids until can
switch to oral glucocorticoids. If animal is in shock, administration of steroids should be at shock doses (prednisolone up to 20 mg/kg) and this should take precedence over establishing an immediate diagnosis.

6) Consider IV glucose and insulin to rapidly lower serum potassium if potassium is greater than 8.5 mequiv/L. This procedure is rarely necessary.

7) Occasionally need to correct acidosis (if serum bicarbonate <12 mequiv/L). Administer 25-50% of calculated dose IV over 6 hours.

8) Mineralocorticoid supplementation:
   - Fludrocortisone (see below for dose)
   - Desoxycorticosterone pivalate (see below for dose)
   - Hydrocortisone

Choice of mineralocorticoid depends upon clinical status of patient (oral versus injectable), product availability, and confidence in diagnosis. In most cases electrolytes normalize with fluid therapy and glucocorticoids alone. Long-term mineralocorticoid therapy can be initiated once the animal is stable and the diagnosis is confirmed. Other treatments that may be indicated in individual patients include synthetic colloids, blood transfusion, and IV dextrose.

**Monitor**

1) Serum electrolytes and acid-base status
2) Urine output
3) ECG
4) Blood pressure
5) Central venous pressure

**Follow-up**

1) Maintain fluids until oral intake possible
2) Continue injectable medication until oral medications can be substituted

**Maintenance Therapy**

Mineralocorticoid:
- Fludrocortisone (0.1 mg/5 kg body weight divided bid)
- Desoxycorticosterone pivalate (2.2 mg/kg IM q 25 days initially).

For either of the mineralocorticoids the dose should be titrated to effect. The dose of fludrocortisone typically needs to be increased over time whereas in many cases the dose of DOCP can be decreased over time. In our clinic we reduce the dose of DOCP by 10% a month provided the electrolytes remain in the normal range at 30 days. In one study the range of doses needed for good control of hypoadrenocorticism ranged from 1.65 to 2.2 mg/kg at intervals ranging from 21-30 days. In our clinic we have used a dose of DOCP as low as 1.0 mg/kg q 30 days for good control of hypoadrenocorticism.

Glucocorticoid:
- Prednisone 0.1 to 0.22 mg/kg initially, then taper dose as low as possible. It is important to avoid excess prednisone supplementation because this may result in clinical signs of hypoadrenocorticism. Only 50% of dogs on fludrocortisone require supplemental prednisone, whereas most dogs on DOCP require prednisone at least every other day.

Dogs with secondary hypoadrenocorticism (glucocorticoid deficiency) only require glucocorticoid supplementation. Treatment for iatrogenic hypoadrenocorticism is drug withdrawal.

**ATYPICAL PRESENTATIONS OF ADDISON'S DISEASE**

Although diagnosis of a typical case of hypoadrenocorticism is usually straightforward, many cases have a less typical presentation. This can result in a missed or incorrect diagnosis, which ultimately may lead to death of the patient, or to marked owner frustration. In a survey of 246 pet owners of dogs with Addison’s disease performed by Novartis Animal Health, 64% indicated that they presented their dog with the problem to 2 or more veterinarians before an accurate diagnosis was made; 18% of owners went to 3 vets, and 12% went to 4 or more vets before the diagnosis was made. In the same survey, 51% of the cases were diagnosed within one week of the time symptoms were first noticed, while 26% took 30 days or more. This data suggests that many veterinarians are failing to include hypoadrenocorticism on their list of differential diagnoses for systemic illness. It is therefore important to be familiar with the “many faces” of this disease.

**Pure glucocorticoid deficiency:** Although most cases of Addison’s disease present with typical electrolyte abnormalities, in some cases the biochemical profile may be completely normal. This is always the case in secondary hypoadrenocorticism, but may also occur with early primary adrenal failure. Some dogs with primary adrenal failure will initially have glucocorticoid deficiency alone and later progress to mineralocorticoid deficiency.
Measurement of an endogenous ACTH concentration will allow differentiation of primary versus secondary hypoadrenocorticism in these dogs and thus allow the clinician to decide whether long-term monitoring of electrolyte concentrations is necessary. Measurement of an increased ACTH concentration confirms a diagnosis of primary hypoadrenocorticism, while an ACTH concentration within or below the reference range this is consistent with a diagnosis of secondary hypoadrenocorticism. Assays for measurement of aldosterone are also available, however they are unreliable in identifying those dogs that will go on to require mineralocorticoid as well as glucocorticoid supplementation.

**Hypoglycemia:** Hypoglycemia severe enough to cause a seizure disorder may occur in hypoadrenocorticism. Other more classic electrolyte changes may or may not be present. Hypoadrenocorticism should always be considered in the differential diagnosis of dogs presenting with hypoglycemia. It is possible that some cases of hunting dog hypoglycemia reported in the past were actually cases of atypical Addison’s disease.

**Severe gastrointestinal hemorrhage:** Severe gastrointestinal hemorrhage may be a feature of hypoadrenocorticism. Causes of gastrointestinal hemorrhage in hypoadrenocorticism may include ischemia due to severe hypovolemia, and the effect of cortisol deficiency on the mucosa of the gastrointestinal tract. Interestingly in one report, dogs with gastrointestinal hemorrhage initially had typical Addisonian electrolyte changes, but by the time of referral had either normokalemia, or hypokalemia. Electrolyte changes typical of hypoadrenocorticism may also occur in dogs with other causes of severe gastrointestinal disease due to hypovolemia and acidosis. Differentiation of Addison’s from other causes of gastrointestinal disease can only be made by the ACTH stimulation test. Dogs with severe gastrointestinal hemorrhage may require blood transfusion(s), and may have prolonged recovery.

**Hepatopathy:** Thirty percent of dogs with Addison’s disease have increased hepatic enzymes, and in addition, hyperlumienemia, hypocolesterolemia, and hypoglycemia are common in this disease. Hypoadrenocorticism may therefore mimic hepatic failure. Abnormalities in liver function tests have also been reported in some Addisonian dogs. It has been speculated that immune mediated hepatitis may occur concurrently with hypoadrenocorticism in some dogs. Alternatively the liver could be secondarily affected due to hypotension and impaired tissue perfusion. Regardless, hepatic abnormalities detected in Addisonian dogs resolve with no specific treatment other than that for hypoadrenocorticism.

**Renal failure:** Azotemia is common in hypoadrenocorticism due to hypovolemia, hypotension, and decreased renal perfusion. Usually renal abnormalities are rapidly corrected with treatment, however a delay in treatment may cause secondary renal damage. Permanent renal failure is uncommon.

**Megaesophagus:** Reversible megaesophagus associated with hypoadrenocorticism has been reported in dogs. The cause of megaesophagus has been suggested to be the effect of abnormal electrolyte concentrations on neuromuscular function, however in some affected dogs electrolyte concentrations are normal.

**Multiple endocrinopathies:** Hypoadrenocorticism may occur in conjunction with other endocrine deficiencies such as hypothyroidism, diabetes mellitus, and hypoparathyroidism. A series of 10 dogs with concurrent hypoadrenocorticism and hypothyroidism have been reported. Hypothyroidism should be considered in any dog with hypoadrenocorticism that has a poor clinical response to initial treatment. In some cases profound hypothyroidism may mask the typical electrolyte changes of Addison’s disease.

**Feline hypoadrenocorticism:** Although not common, hypoadrenocorticism also occurs in the cat. Clinical signs and laboratory abnormalities are similar to those reported in the dog. Response to treatment is similar although clinical signs such as anorexia, lethargy, and weakness may persist for longer in the cat. Adrenal destruction due to lymphoma should be considered in the differential diagnosis of Addison’s disease in the cat.

**Summary**

Hypoadrenocorticism is a complex illness that has been rightly labeled the “Great Pretender”. Dysfunction of the adrenal gland should be considered as a potential differential diagnosis in any dog or cat presenting with acute or chronic systemic illness. The diagnosis should never be excluded based on the presence of normal electrolytes. Appreciation of the myriad ways that an Addisonian patient may present should increase the index of suspicion for this disease and decrease the likelihood of us missing the boat.

**References**