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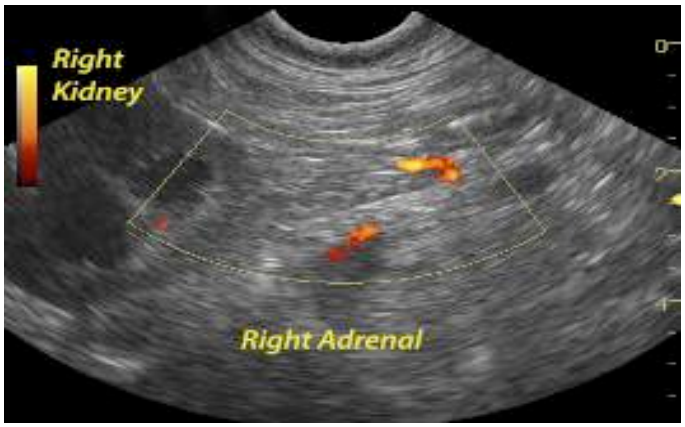
Addison's – 4 Pages



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Naturally occurring primary hypoadrenocorticism is a relatively uncommon condition in both dogs and cats characterized by clinically significant loss of adrenocortical secretory capacity. However, recent research by SonoPath.com and collaborators on sonographic criteria for Addisonian adrenal glands may suggest and increased frequency of atypical Addison's disease in dogs.

ETIOLOGY

Impaired adrenocortical function may develop as a result of disease of any part of the hypothalamic-pituitary-adrenal axis. However in dogs, hypoadrenocorticism is generally a result of substantial destruction of adrenocortical tissue. Although any destruction of adrenocortical tissue may impair adrenocortical reserve, in non-stressful situations approximately 90% of the adrenal cortex needs to be non-functional before this impairment becomes clinically significant.

In most cases the underlying reason for adrenal destruction appears to be idiopathic or immune-mediated. A genetic predisposition for hypoadrenocorticism has been demonstrated in Standard Poodles, Bearded Collies and Nova Scotia Duck Tolling Retrievers. Additionally there are a number of other breeds where hypoadrenocorticism is encountered more commonly than would be expected. Female dogs are also more commonly affected with a ratio of approximately 2:1.

Over dosage and/or idiosyncratic reactions in dogs with hyperadrenocorticism treated with mitotane or trilostane can also result in either temporary or permanent hypoadrenocorticism.

CLINICAL FEATURES

Hypoadrenocorticism has been reported in dogs ranging from 2 months to 14 years of age, although most affected animals are young to middle age. The clinical features vary from acute collapse to non-specific signs that suggest the animal is unwell but do not focus the clinician's attention on any particular body system or particular characterizing feature.

Patients presenting with acute collapse usually have evidence of generalized, marked hypovolemia and dehydration, together with vomiting, diarrhea, abdominal pain and hypothermia. Some may have severe gastrointestinal hemorrhage with melena and occasional hematemesis. Although affected animals may have an inappropriately low heart rate for their degree of circulatory collapse and indeed some may even be bradycardic, the chronotropic drive induced by the hypovolaemia means many severely affected individuals will be tachycardic. It is not uncommon for dogs with primary hypoadrenocorticism to have a waxing and waning illness characterized by variable gastrointestinal signs and depression/weakness interspersed with periods of apparent normality before they present in a collapsed state.

All dogs with primary hypoadrenocorticism are potentially unstable as they are variably hypovolemic and thus prone to marked hypotension. This hypotensive potential is due to a lack of aldosterone secretion which is possibly further exacerbated by concurrent decreased vascular responsiveness to normal pressor effects.

Differential Diagnosis

For the cardinal features of the disease, i.e., rapidly worsening depression, weakness, anorexia and vomiting, there are only a limited number of syndromes that may have a similar picture. These are ileus, acute renal failure, acute gastroenteritis and acute pancreatitis. Initially the differentiation may pose problems as the other conditions occasionally are associated with electrolyte disturbances as well.

DIAGNOSIS

Hematology

In the presence of appropriate clinical signs, suspicion for hypoadrenocorticism is dramatically increased by the presence of lymphocytosis and/or eosinophilia or simply the absence of a stress leukogram in a clearly "unwell" patient.

Acute hypoadrenocorticism commonly results in a non-regenerative or variably regenerative anemia which may be profound in those cases with severe concurrent gastrointestinal hemorrhage. Often the magnitude of the reduction in packed cell volume underestimates the severity of the true anemia because of the concurrent hypovolaemia/dehydration. If severe enough, gastrointestinal hemorrhage may result in a regenerative anemia.

Biochemistry

The most consistent biochemical abnormalities include azotemia, hyponatremia, hyperkalemia, hypochloremia and less commonly hypoglycemia and hypercalcemia. Hyponatraemia and hyperkalaemia with a sodium: potassium ratio of less than 23:1 are considered characteristic features of primary hypoadrenocorticism, although fluid shifts (body cavity effusion, GI tract) may give a similar ratio.

Additionally, approximately 10% of dogs with primary hypoadrenocorticism have reference range electrolyte concentrations or only mild hyponatremia without hyperkalemia at the time of diagnosis. These animals have either early or mild primary hypoadrenocorticism or, more commonly, selective "glucocorticoid deficient hypoadrenocorticism". Consequently the diagnosis of hypoadrenocorticism cannot be precluded in animals with normal or mild electrolyte changes.

As with all hypovolemic conditions, animals with primary hypoadrenocorticism develop azotemia as a consequence of poor renal perfusion. However unlike other hypovolemic conditions where renal concentrating ability is maintained, dogs with primary hypoadrenocorticism are generally unable to concentrate their urine effectively. Impaired urine concentrating ability is due to mineralocorticoid deficiency and resultant chronic renal sodium loss, depletion of normal renal medullary sodium concentration gradient and impaired water resorption from the renal collecting ducts. As a consequence, azotemia is usually accompanied by inappropriately dilute urine increasing the potential for affected animals to be mistakenly

Supplementary Diagnostic Aids

Other diagnostic aids that may provide supporting evidence for hypoadrenocorticism as well as ruling out other causes include electrocardiography, thoracic radiography and abdominal ultrasonography.

ACTH stimulation test

A definitive diagnosis of spontaneous hypoadrenocorticism requires the demonstration of subnormal basal and post-ACTH plasma cortisol concentrations. As hydrocortisone, prednisolone and prednisone all cross-react in cortisol assays it is essential that the ACTH response test be performed before these agents are administered. In contrast, dexamethasone does not cross-react in the cortisol assay and consequently can be used to provide glucocorticoid support to critically ill patients if the clinician is concerned about leaving the patient without glucocorticoid supplementation until the ACTH response test has been completed. However dexamethasone does directly inhibit endogenous cortisol production however this usually takes at least 4-6 hours to take effect. Consequently any artifactual lowering of post ACTH cortisol levels can be avoided by insuring the ACTH response test is completed within 2-3 hours of dexamethasone administration.

TREATMENT

Because of the combination of a potentially critical patient and the inability to confirm a diagnosis by cortisol estimation within hours of hospitalization, there are frequently times when suspected hypoadrenocorticism requires treatment before a diagnosis has been reliably confirmed. Initially most affected animals require concurrent intravenous fluid and parenteral glucocorticoid/mineralocorticoid replacement therapy.

Initial Stabilizing Therapy

Fluid therapy should be started as soon as possible in the acutely sick patient. Patients with hypoadrenocorticism are susceptible to fluid overload and additionally rapid correction of the hyponatremia may result in neurological disease and myelinolysis characterized by a variety of variably reversible neurological signs. There is thus a conflict between the need to rapidly correct the severe hypovolemia while insuring the serum sodium concentration does not increase rapidly. The fluid of choice is physiological saline at an initial rate of 10-30 ml/kg/hr with a subsequent reduction to no more than twice maintenance levels (120 ml/kg/24 hours) after 2-3 hours. Because of the potential for excessively rapid correction of the hyponatremia, plasma sodium concentration should be monitored closely.

Although fluid therapy generally results in a marked reduction in plasma potassium, restoration of renal perfusion and correction of acidosis it should be complemented by treatment with a parenteral agent possessing both glucocorticoid and mineralocorticoid activity. Hydrocortisone sodium succinate (HSS) is currently the only commercially available parenteral steroid with equipotent glucocorticoid and mineralocorticoid activity. Although soluble dexamethasone or prednisolone preparations can be used, the lack of mineralocorticoid activity makes them less attractive alternatives to HSS.

Maintenance Therapy

Once the patient is stabilized, glucocorticoid and mineralocorticoid replacement therapy is almost always needs to be maintained for the remainder of the animal's life. Traditionally, a mineralocorticoid and a glucocorticoid are initially used together.

Fludrocortisone acetate is a synthetic adrenocortical steroid with both glucocorticoid and mineralocorticoid potency. Fludrocortisone has 10 times the glucocorticoid activity and 125 times the mineralocorticoid activity of cortisol. The dose of fludrocortisone is 10 to 30 µg/kg administered orally once daily. Typically a lower dose is used initially with subsequent titration based on clinical impression and plasma electrolyte concentrations. Dose adjustments are usually made after weekly electrolyte evaluations. Once these are stable and within the normal range adjustments can be made every 3-4 months.

In patients receiving concurrent long-term fludrocortisone and prednisolone, it is not uncommon for the dose of fludrocortisone to gradually increase, as there appears to be a reduction in its mineralocorticoid efficacy over time. Although many possible mechanisms for this exist, it is tempting to speculate that this represents accelerated metabolism of both steroids in response to the chronic "supraphysiological" state created by long-term daily prednisolone administration.

Desoxycorticosterone pivalate is a potent long-acting mineralocorticoid with little if any glucocorticoid activity. The recommended dose of DOCP is 2.2 mg/kg by deep intramuscular injection every 25 days

and creatinine concentrations are monitored every two weeks to determine the duration of action and help individualize the dose. Once stabilized it is prudent to check electrolytes every 3-6 months. Most dogs are well controlled on 1-2 mg/kg every 3-4 weeks although it has been suggested that occasional individuals will require more frequent dosing. As DOCP has no glucocorticoid activity it is essential that patients receive concurrent glucocorticoid supplementation with either cortisone acetate or prednisolone.

Cortisone acetate is a synthetic steroid that once absorbed is rapidly activated to hydrocortisone and then to cortisol. As it has equipotent glucocorticoid and mineralocorticoid activity it will also provide more mineralocorticoid activity than other synthetic glucocorticoids such as prednisolone. In addition, its shorter half-life and lower overall activity means it may be less likely to create iatrogenic hyperadrenocorticism with long-term administration.

In patients with hypoadrenocorticism, orally administered cortisone acetate can be used as an effective long-term cortisol replacement. The dose of cortisone acetate must be individualized according to the severity of the condition, the response obtained and what other glucocorticoid or mineralocorticoid is being concurrently administered. In the changeover period as animals recover from an acute crisis, start eating and drinking and are changed from parenteral to oral medication most hypoadrenocorticoid dogs are started on a dose of 0.5-1 mg/kg/12-24hr. However once they are stable, generally a dose of 0.5 mg/kg/12-24 hr provides adequate additional glucocorticoid supplementation.

Prednisolone is a synthetic adrenal steroid with moderately potentiated glucocorticoid activity (approximately 5 times that of hydrocortisone) and less than 10% of hydrocortisone's mineralocorticoid activity. Some clinicians advocate its use as a glucocorticoid supplement in the long-term management of hypoadrenocorticism at a dose rate of between 0.2-0.5 mg/kg/24hr.

Dr. Remo Lobetti (DECVIM, PhD) is a world renowned speaker in internal medicine and infectious disease and also a daily collaborator to the SonoPath.com diagnostic efficiency project. You may find more information on Dr. Lobetti at www.SonoPath.com

The May case of the month at SonoPath.com shows a sonographically diagnosed case of atypical Addison's disease. An ongoing study on sonographic criteria of Addisonian adrenal glands is under way at SonoPath.com and recently submitted for abstract for ECVIM 2011, Seville, Spain by Lindquist, Frank, Marek, & Timon

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"Make every obstacle an opportunity." Lance Armstrong