

Equine Cushing's Disease

Mark T. Donaldson, VMD, DACVIM

New Bolton Center, School of Veterinary Medicine, University of Pennsylvania

Equine Cushing's disease (ECD) is one of the most common equine endocrinopathies. In one report of horses admitted to a university teaching hospital it accounted for 0.5% of all admissions and in the primary care equine ambulatory practice at the University of Pennsylvania, approximately 4.5% of horses over 15 years old were diagnosed with ECD. There may be several reasons for the apparent increase in the frequency of ECD. First, advances in equine health care have prolonged the useful life of horses and therefore, there is an expectation the horses will remain active into their late teens and early twenties. Second, there has been an increase in the availability of convenient diagnostic methods and treatments for ECD.

Equine Cushing's disease results from excessive secretions of pro-opiomelanocortin (POMC) derived peptides from the pituitary pars intermedia (PI). Unlike the pars distalis, which is the most common location of pituitary tumors in dogs, the PI does not have a negative feedback response to cortisol and is not stimulated by corticotropin releasing hormone.

Pro-opiomelanocortin is processed into beta-endorphin (beta-END), melanocyte stimulating hormone (MSH), corticotropin-like intermediate peptide (CLIP) and ACTH. Although the effects of ACTH have received much attention, other POMC-derived peptides are disproportionately higher and may have important implications in the pathogenesis of ECD. For example, both MSH and beta-END are immunomodulators. Furthermore, POMC-derived peptides potentiate the effect of ACTH.

Normal horses have a diurnal variation in the cortisol secretion, with a peak in the morning and a nadir in the evening. This diurnal variation may be lost in horses with ECD, leading to an increase in total daily cortisol secretion.

Recently, it has been suggested that cortisol metabolism may be altered at the cellular level to produce some signs of ECD, such as obesity and laminitis, in horses with a normal hypothalamic-pituitary-adrenal axis. This "Peripheral Cushing's Syndrome" warrants further investigation.

The clinical signs and progression of ECD are extremely variable. Some horses show numerous clinical signs consistent with the disease while others may only demonstrate one aspect. The progression of ECD is slow in most cases. Some owners report clinical signs of ECD, such as abnormalities in the hair coat or episodes of laminitis, that had been present for 10 years or more before diagnosis. Rarely, a horse will develop laminitis and deteriorate rapidly without showing other signs of ECD.

The average age at diagnosis in retrospective studies of ECD is 20 years. However, in my experience, which is consistent with the reports of clinical signs of the disease that are present for years prior to diagnosis, the onset is much earlier. Many horses appear to develop the first signs of ECD in their early to mid teens. Although a breed predisposition

has not been identified, it is rare in thoroughbred horses in my experience. Ponies are commonly affected, perhaps due to their longer life span.

Although the most common and striking clinical sign of ECD is hirsutism, it is important to remember that not all horses with ECD have hirsutism. Horses with ECD may shed out their winter coats later in the spring when compared to normal horses maintained under similar conditions. Similarly, they may develop a heavy coat earlier in the fall. The hair may be longer than normal, especially in the ventral neck and distal limbs. Furthermore, it may be wavy, dull and lighter in color.

Laminitis is one of the most common presenting complaints. Although the onset of pain may be acute, examination of the hoof frequently reveals ridges that suggest the presence of sub-clinical chronic laminitis. Laminitis is the most common cause for euthanasia and the most serious sequela of ECD. Several studies on the epidemiology of laminitis have shown that older horses are at increased risk for laminitis but the cause of laminitis was not investigated in these studies. In a retrospective study of laminitis in the equine ambulatory practice of the University of Pennsylvania, the majority of horses with laminitis had ECD. The average age was 15 years and many of these horses did not have other clinical signs of ECD.

Horses with ECD develop laminitis by several mechanisms. Cortisol sensitizes vascular endothelium to the effects of catecholamines. Because corticosteroids are catabolic hormones, it is possible that the integrity of the laminar bond is compromised. Since horses with ECD are insulin resistant, it is noteworthy that inhibition of glucose metabolism results in a laminar separation in an in vitro model of laminitis.

Alteration in body fat distribution is common in horses with ECD. As in people with Cushing's disease, horses with ECD accumulate fat in the neck giving it a "cresty" appearance. The back, tail head and supraorbital fossa are also affected. In spite of accumulation of fat in these areas, the ribs can be seen highlighting the abnormal distribution of fat. In later stages of the disease when metabolic derangements become severe, a generalized loss of fat and muscle occur, leading to an overall poor body condition.

Unfortunately, many owners (and veterinarians) may attribute the lethargy of an older horse to a natural process. However, with treatment for ECD, temperament and activity level improve, suggesting POMC derived peptides affect behavior. Both corticosteroids and beta-endorphin may be responsible for these behavioral changes.

Other clinical signs associated with ECD include hyperhidrosis, tachypnea, PU/PD, immunosuppression, blindness, abnormal mammary gland development, delayed wound healing, seizures and infertility. Hyperhidrosis frequently occurs around the chest and neck and occurs in horses with and without hair coat changes. It is also beneficial to question owners about hyperhidrosis as this may occur only intermittently. Episodes of tachypnea are rare in my experience but dramatic when they occur. Respiratory rates can be as high as 90 breaths per minute and a shallow pattern mimics a horse recovering from intense exercise. The pathogenesis is unclear but arterial blood gases have been normal in two horses I have examined, suggesting a central lesion. Polyuria and polydipsia may go undetected if the horse is pastured. It is also important to question those caring for the

horse (if not the owner) about the presence of polyuria or polydipsia. Polyuria and polydipsia may be secondary to severe hyperglycemia and osmotic diuresis or the direct effects of cortisol on renal function. Large pituitary adenomas may also compress the anterior pituitary, resulting in a loss of ADH secretion and diabetes insipidus. Immunosuppression is most frequently manifested by parasitism; thus, horses with ECD should receive regular anthelmintics. The advanced age of most horses with ECD is associated with poor dentition and secondary sinusitis. Dermatophilosis may be exacerbated by hirsutism and hyperhidrosis. Recent studies on the epidemiology of EPM suggest older horses are at increased risk, consistent with the possibility of subclinical ECD. Rarely, enlargement of a pituitary adenoma may cause compression of the optic chiasm and blindness. Abnormal mammary gland development may be due to prolactin secretion, which is also under dopaminergic inhibition.

The association between infertility and ECD is unclear. Although some mares clearly affected with ECD are able to conceive and deliver normal foals, other apparently less severely affected mares have difficulty conceiving. Some clinicians report that mares with ECD will have a cervix that does not relax during estrus.

In general, the clinical manifestations of ECD are difficult to predict. Some horses with severe hirsutism that may have been present for many years do not show evidence of laminitis while other horses without any other clinical signs of ECD develop laminitis and deteriorate rapidly.

Clinical laboratory abnormalities associated with ECD include hyperglycemia, increased liver enzymes, neutrophilia, lymphopenia and anemia. The presence of hyperglycemia is concerning as it suggests that homeostatic mechanisms are overwhelmed by the disease. Although most horses with ECD are hyperinsulinemic and insulin resistant, hyperglycemia may result from pancreatic beta cell exhaustion or rarely, pancreatitis and secondary insulin insufficiency.

Among the various diagnostic methods for ECD, the dexamethasone suppression test (DST) has the highest sensitivity. Because the pars intermedia does not have a negative feedback response to glucocorticoids, there is a rational physiological basis for the test. Forty micrograms per kilogram of dexamethasone are given IM between 4 and 6 p.m. Blood is taken before dexamethasone is given and between 10 a.m. and noon the following day (approximately 19 hours later) and assayed for cortisol. Post-dexamethasone cortisol levels above 10 ng/ml are diagnostic of ECD.

Because of the association between laminitis and corticosteroids and the frequency of laminitis in horses with ECD, some clinicians avoid the DST. Basal ACTH concentration is convenient, provides a good alternative to the DST and in most cases a single sample is diagnostic. Proper handling of samples is critical. Blood is usually collected with EDTA as an anticoagulant and it should be kept cold until plasma is separated, which should occur within three hours after collection. It should then be frozen and assayed as soon as possible. It is best to consult with the laboratory before sampling. It is important that laboratories develop their own normal values, as there is tremendous variation between laboratories. The sensitivity of basal ACTH concentrations has been reported to be from 82% to 100%. Although a high ACTH concentration is diagnostic, a normal ACTH

concentration may be a false negative and therefore, if clinical signs are consistent with ECD, the basal ACTH should be repeated or a DST should be performed. In my experience, there does not appear to be a correlation between ACTH concentration and prognosis or severity of clinical signs. Furthermore, we have observed large variations in basal ACTH concentrations from day to day. Couetil reported significantly lower ACTH concentrations in ponies when compared to horses. Until further research refutes this finding, one should use caution interpreting basal ACTH concentrations from ponies when submitted to a lab that does not recognize this difference. False negative results may occur if samples from ponies are interpreted using the normal values developed from a population of horses. The effects of severe stress, pain or concurrent illness on ACTH concentrations have not been critically evaluated.

Insulin concentrations may be increased in ECD but they are not specific for this disease. Obesity and recent feeding may cause an increase in insulin concentration. It has been hypothesized that abnormal metabolism of cortisol at the cellular level ("Peripheral Cushing's Syndrome") may also result in hyperinsulinemia. Because insulin concentrations vary greatly throughout the day, single samples may be misleading.

Basal cortisol may be high, low or normal and has little diagnostic value. The significance of a loss of diurnal rhythm in the diagnosis of ECD is controversial. Although some laboratories advocate its use, it has not been critically investigated as a diagnostic technique and false positives are possible. For example, diurnal rhythm is lost in horses that are moved from their normal environment.

The TRH stimulation test is a valuable test that was developed as an alternative to the DST. In horses with ECD, cortisol increases inappropriately in response to TRH administration. However, some false negative results have been reported when basal hypercortisolemia is present.

The association between ECD and hypothyroidism is intriguing. Because the body fat changes that accompany ECD are similar to the signs of hypothyroidism in other species, many horses with ECD have been diagnosed as hypothyroid based on low basal thyroid hormone concentrations. This may be partially due to the availability of assays for thyroid hormones that were available long before assays for ACTH in the horse were validated. Most horses with ECD have low thyroid hormone concentrations. Stimulation with TRH usually results in an appropriate increase in T3 and T4, suggesting a normal pituitary thyroid axis and implicating a hypothalamic lesion or the euthyroid sick syndrome. The need for thyroid supplementation is not clear; however, supplementation is unlikely to be detrimental.

Hypothyroidism has also been anecdotally associated with infertility. However, there was no correlation between thyroxine concentration and pregnancy in a study of over 300 broodmares.

Management of horses with ECD includes clipping long hair coats, which some authors have suggested may prevent pneumonia. Owners should be vigilant about deworming, pasture management and hoof care. Because horses with ECD are insulin resistant, diets high in carbohydrate should be avoided. This includes access to lush pastures. Obese

horses with ECD appear to be especially predisposed to laminitis and therefore, grazing muzzles are useful. I avoid modified live vaccines in horses with ECD due to the potential for adverse effects associated with immunosuppression.

Horses that have metabolic derangements (hyperglycemia or increased liver enzymes) or those that have laminitis or evidence of immunosuppression should be treated. Although many horses live for years without treatment for ECD, it is difficult to predict when a serious complication of the disease may occur. Owners of horses with ECD should be aware of potential complications so that an informed decision regarding treatment options can be made.

Several studies have shown that pergolide is an effective treatment for ECD. Improvements in clinical signs, DST results and ACTH concentrations occur during treatment. It is a dopamine agonist which is thought to inhibit POMC-derived peptides; however it, is unreasonable to expect the complex hypothalamic mechanisms that regulate PI function to return to normal. Therefore, some horses maintain an abnormal hair coat. Although doses as low as 0.75 mg/450 kg q 24 h may cause an improvement in the DST, in one report, we found that an average dose of 1.5 mg/450 kg q 24 h was necessary to return ACTH concentration to normal. I start treatment with pergolide at 1 mg/ 450kg PO q 24 h, evaluate ACTH concentration in 4 weeks and increase the dose by 0.5 mg until ACTH is normal and clinical signs have resolved. ACTH concentration is then evaluated every 6–12 months depending on the recurrence of clinical signs. In general, long-term treatment doses not appear to result in a need for an increase in dose. There is a correlation between pergolide dose and post treatment ACTH concentration. I have had good success with compounded formulations of pergolide.

Since pergolide is a dopamine agonist, it may suppress prolactin secretion in a manner similar to ergot alkaloids found in endophyte-infested fescue. Broodmares that require pergolide treatment due to metabolic derangements or infertility should be treated until one month before the anticipated date of foaling.

Cyproheptadine, a serotonin antagonist, has been used in the treatment of ECD with variable results. It is given at 0.25 mg/kg PO q12-24 h. The rationale for treatment is unclear and serotonin concentrations in the PI of affected and normal horses are similar. It is possible that its purported clinical effect is unrelated to PI function. Most studies show that pergolide is a superior treatment with more frequent improvements in biochemical parameters and clinical signs. It is difficult, however, to evaluate clinical signs in response to treatment since the progression of the disease is in many cases very slow with periods of transient spontaneous improvement.

Hormonise is the trade name for an extract of chaste berry (*Agnus castus*). Extracts of this plant have been shown in vitro to contain a dopamine agonist. Therefore, one would suspect that it might be an effective treatment for ECD. Anecdotal reports have claimed it to be effective. We treated 15 horses with Hormonise according to the manufacturer's recommendation and did not see improvement in ACTH concentration, DST results or clinical signs in any horses.

References available upon request.