Proceedings of the 9th International Congress of World Equine Veterinary Association

Jan. 22 - 26, 2006 - Marrakech, Morocco

Reprinted in IVIS with the permission of the Conference Organizers http://www.ivis.org/
EQUINE CUSHING'S DISEASE: DIAGNOSIS AND TREATMENT

Couëtil L.L.
School of Veterinary Medicine, Purdue University, West Lafayette, Indiana, USA

Summary

Equine Cushing's Disease (ECD) is commonly encountered in older horses and ponies. The condition results from a pituitary gland adenoma which secretes abnormally high levels of adrenocorticotropin (ACTH) as well as other hormones. Although, ECD clinical signs are often typical, reaching a definitive diagnosis is frequently difficult. Currently, the most sensitive and specific tests for ECD diagnosis are Overnight Dexamethasone Suppression Test (ODST) and basal plasma ACTH concentration. The latter has the advantage of requiring only one blood sample and being a useful test for treatment monitoring. Medical therapy with cyproheptadine or pergolide is fairly effective at controlling clinical manifestation of ECD including laminitis. A combination of careful health management, preventative medicine and medical therapy of ECD can significantly improve comfort and life expectancy of affected horses and ponies.

Introduction

Benign tumors involving the pituitary gland are commonly reported during post-mortem examination of elderly horses.(1) These pituitary adenoma produce a recognized disease in older horses called Equine Cushing's Disease (ECD) or pituitary pars intermedia dysfunction.(2) Both human Cushing's disease and the equine clinical syndrome are characterized by excessive adrenocorticotropin (ACTH) production from a pituitary tumor resulting in abnormally elevated cortisol secretion (hyperadrenocorticism).(3; 4)

Although ECD clinical signs in advance cases have striking features, diagnosing pituitary adenoma has always been a challenging task for veterinarians. Furthermore, little is known about clinical response and prognosis and ECD treatment is often regarded as poorly effective. This review outlines recent developments in diagnosis and treatment of ECD.

Pathophysiology of ECD

The equine pituitary gland produces various hormones and some of them have a common precursor protein called pro-opiomelanocortin (POMC). The breakdown of this precursor molecule differs according to the particular regions of the adeno-hypophysis.(3; 4) In the pars distalis, POMC is processed into adrenocorticotropin (ACTH), ß-endorphin (ß-END), and several other peptides. The processing is more complete in the pars intermedia where most of the ACTH will be broken down further into _-Melanocyte-Stimulating Hormone (_-MSH) and Corticotropin-Like Intermediate lobe Peptide (CLIP). Therefore, less than 2% of ACTH production originates from the Pars Intermedia.

The hypothalamus synthesizes Corticotropin Releasing Factor (CRF) and Arginine-Vasopressin (AVP) which regulate ACTH secretion from the pars distalis.9,10 However, the pars intermedia is minimally influenced by humoral secretions and is mainly controlled by neurotransmitters directly released from hypothalamic neurons. Currently, dopamine appears to be the primary neurotransmitter responsible for tonic inhibition with additional control by serotonin.(2; 3) Plasma ACTH stimulates cortisol production from adrenal glands and in return cortisol inhibits ACTH production by acting at both the pituitary and hypothalamic levels. However, pars intermedia ACTH production seems unaffected by glucocorticoid (GC) negative feedback.

Studies have indicated that POMC processing in pars intermedia tumors of horses with ECD was similar to that in the normal pituitary gland.(3; 4) However, in affected horses or ponies more POMC is present
for processing which results in elevated breakdown products. In particular, plasma ACTH concentration is significantly high in cushingoid equids.\(^3\)\(^-\)\(^5\) The increase peptide processing appear to result from reduced dopaminergic neurons that normally inhibit secretion from the pars intermedia. Hyperadrenocorticism plays a major role in the pathogenesis of Cushing's disease, but the role of the other POMC-peptides is unknown.

**Clinical signs**

The average age of Cushingoid horses is 19 years with a range of 7 to 40 years.\(^2\) There is no sex or breed predisposition, but some authors report that ponies appear to develop this disease more frequently.

Among the wide variety of clinical signs associated with ECD, the most common is hirsutism, reported in more than 85% of cases. In addition to the typical long shaggy hair coat that is not shed, a variety of other hair coat abnormalities can occur. For instance early sign of ECD can be delayed shedding in the spring usually followed by an early re-growth of winter coat in the fall. Or, incomplete shedding can appear as long hairs under the shins, belly, on the legs, or in few round patchy areas all over the body. Although not pathognomonic, these abnormal hair coat patterns are highly suggestive of ECD. Other possible differential diagnoses for hirsutism are breed variation (e.g. foxtrotter, bashkin) and adrenal insufficiency.

Repeated bouts of laminitis for unknown reasons and that are refractory to conventional therapy, are commonly observed. Excess circulating cortisol has been linked to this manifestation, however, its pathogenesis is not well understood. Intractable pain secondary to laminitis represents the leading cause of euthanasia in Cushingoid horses.

Horses with ECD are predisposed to chronic infections and delayed wound healing. Chronic sinusitis, pneumonia, refractory skin infection and muco-purulent conjunctivitis are among the most commonly observed manifestations. Hypercortisolism is a likely etiology, however POMC peptides regulatory effects on equine cell mediated immunity may also be involved.

Body condition is often good, some ECD cases even exhibit a "creesty" neck and obese appearance. As the disease progresses, weight loss, muscle wasting and muscle weakness become apparent and lead to the typical pot-bellied appearance. Poor body condition is often potentiated by internal parasitism, poor appetite secondary to buccal ulceration, and redistribution of body fat (e.g. bulging supra orbital fat pads). In addition, Weight loss may result from conditions unrelated to ECD but often encountered in older horses such as poor dentition or, an inadequate feeding regimen.

Polyuria-polydipsia (PUPD), hyperhydrosis and lethargy are also commonly described in patient with ECD. Infrequently reported clinical signs are visual deficits, abnormal estrus activity, tachycardia, tachypnea and hypertrophic osteopathy.

**Clinical pathology and diagnostic tests**

Hematology and blood chemistry findings are usually unremarkable. Although insulin-resistant hyperglycemia is commonly seen in Cushingoid horses, stress induced hyperglycemia in normal horses may result in glucose levels of the same order of magnitude. In addition, up to 54% of cushingoid horses are normoglycemic.\(^5\)

Endocrine tests like plasma cortisol level, ACTH stimulation test and combined dexamethasone-cosyntropin test often yield ambiguous results and therefore have poor sensitivity.\(^2\);\(^5\);\(^6\) Basal insulin level, glucose tolerance test and insulin response have good sensitivity however, they are only applicable to horses with abnormal glucose regulatory mechanisms i.e. hyperglycemia. Furthermore, hyperglycemia with normal basal insulinemia has been reported in a horse with a pituitary tumor. In addition, ponies often have a relative insensitivity to insulin in comparison to horses.\(^6\)
The Thyrotropin-Releasing Hormone (TRH) stimulation test results in a significant increase in plasma cortisol in equids with ECD as compared to normal horses. However, specificity and sensitivity of TRH stimulation test for ECD diagnosis are unknown.

The overnight dexamethasone suppression test (ODST) has good sensitivity and specificity for ECD diagnosis (100%) and has been reported to be safe. The test protocol requires basal cortisol measurement at 5 PM followed by dexamethasone injection (40 _g/kg, IM). The ODST has the best sensitivity if the post-dexamethasone sample for cortisol measurement is collected at noon the next day (19 hours later).

In humans, high plasma ACTH concentrations are suggestive of pituitary adenoma and similar results were found in cushingoid horses.(3-5)

Recently, several commercially available human ACTH assay have been validated for horses. In order to obtain reliable ACTH measurement, the blood has to be drawn in an EDTA tube and the plasma has to be separated within 3 hours of blood collection. These first 2 steps can be done at ambient temperature without significantly affecting the ACTH measurement. Then, the plasma should be frozen at -20°C in a plastic tube (polypropylene) and can be kept up to 1 month before being assayed. Samples of frozen plasma should be shipped to the appropriate laboratory on dry ice over-night to ensure that they do not thaw during shipment. The ACTH test sensitivity and specificity are good. Plasma ACTH values above 50 pg/ml for horses and ponies are highly suggestive of ECD. Plasma ACTH concentrations between 35-50 are equivocal and regroup early cases of ECD or normal but stressed equids. Also, recent data indicate marked seasonal changes in plasma ACTH concentration of healthy horses and ponies with levels as high as 200 to 400 _g/ml during the Fall season.(7) In these cases, animals should have their ACTH level reassessed and/or have an ODST performed.

**Treatment**

Treatment of ECD should concentrate primarily on careful health management and preventative medicine. Particular attention should be paid to diet, vaccination, deworming, teeth maintenance, hooves trimming and prompt response to infection. Cushingoid horses with long hair coat should be clipped during the warm season. In addition, because of their decreased ability to acclimate to temperature variations they should be provided with shelters or appropriate blankets during cold weather. Good quality feed, easily chewable for horses with poor dentition, is important. On the other hands one must avoid overfeeding which would increase the risk of laminitis in animals already predisposed to it. Laminitis is probably the most difficult complication to deal with. However, it appears that medical therapy for ECD brings a substantial improvement in patient comfort and decreases the likelihood of further bouts of laminitis.

Medical therapy uses three drug families: dopamine agonists (bromocriptine, pergolide), serotonin antagonists (cyproheptadine) and adrenocorticolytic drugs (trilostane). Bromocriptine administered either orally or subcutaneously has been shown to mildly decrease plasma ACTH and cortisol levels however, oral absorption is poor.(3) The successful long-term management of a cushingoid pony with either injectable or oral bromocriptine at doses ranging from 0.03 to 0.09 mg/kg twice daily has been reported.

Oral pergolide has similar properties and clinical improvement has been reported in 90% of cushingoid horses and ponies treated. Initial dose should be low (0.25 to 0.5 mg/day in a 250-500 kg horse) and the increment progressive (0.25 to 0.50 mg every 3-4 days) in order to avoid side effects.(8; 9) Clinical response is usually noted within several weeks at doses varying from 1 to 5 mg/day. If anorexia, colic or other side effects develop, pergolide dose should be decreased until they resolve.
Cyproheptadine has been used successfully in horses and ponies with pituitary dependent Cushing's disease. (2; 6) I currently start therapy with cyproheptadine orally at 0.25 mg/kg, once a day, for 1 month and then measure plasma ACTH again. If plasma ACTH is similar to the previous value or higher, I increase the dosage to 0.25 mg/kg twice a day and repeat the test in a month. If plasma ACTH is decreased and clinical signs improved, cyproheptadine is maintained at the same dose and ACTH is assessed every 2-4 months or if clinical signs worsen. Few horses were treated with higher doses (0.3 to 0.5 mg/kg per os, q 12 hours) however, it seems that horses that do not respond clinically to 0.25 mg/kg q 12 hours are unlikely to do so with higher dosages.

Among 16 horses and ponies with a clinical diagnosis of ECD that I treated with cyproheptadine and followed clinically, 75% improved within 2 months of therapy. ACTH level decreased in 70% of cases one month after treatment was started. However, plasma ACTH concentration rarely returned within the normal range. The earliest sign of clinical improvement appears to be the hair coat, which in some cases, started to shed 10 days after treatment initiation. Later, water consumption may normalize. Discomfort secondary to laminitis improved in 60% of treated horses over a period of a few weeks. In the meantime, laminitis was treated conventionally with corrective shoeing and medical therapy (phenylbutazone, isoxsuprine). This treatment prevented objective assessment of cyproheptadine efficacy in managing laminitis in cushingoid horses. However, most of the affected horses or ponies were treated for chronic laminitis with conventional therapy prior to cyproheptadine and clinical response was considered poor.

Prognosis is highly dependent on disease stage and the severity of clinical signs (i.e. laminitis). However, Dybdal reported following several horses for as long as 10 years after ECD had been diagnosed. (2)

Trilostane (0.4 - 1 mg/kg, PO) has been shown to improve clinical signs in horses with ECD. (10) In this study, therapy ameliorated clinical signs such as lethargy (19 of 19 horses), laminitis (13/16), PUPD (11/11), and coat quality (6/20) within 30 days of treatment initiation. Clinical improvement was not accompanied by reduction in serum cortisol concentration.

Although limited data exists on the prevalence of ECD, increased awareness of this condition and the availability of practical diagnostic tests should result in a more common recognition of the condition in horses and ponies. In addition, appropriate treatment and follow-up should improve life expectancy of cushingoid equids.

References


