



Many horse people are familiar with the classical symptom of advanced Cushing's disease in horses: a shaggy coat that refuses to shed out in the spring. But did you know that this hormonal disease can cause significant medical problems for your horse long before the typical haircoat changes occur? If you own horses in their teens or twenties and wish to help them maintain optimal soundness and vigour as they age, attend this presentation to learn more about the early warning signs of Cushing's disease, as well as the latest insights into its diagnosis and treatment.

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Introduction

With each passing year, horses are living longer lives and their owners are becoming more interested in preserving health, athletic capability, and quality of life throughout middle age and the geriatric years. The purpose of this article and conference presentation is to review the key features of equine Cushing's disease, an endocrine disorder that is common among aged horses. Affected horses appear older than their age would suggest and exhibit a variety of medical symptoms and complications, including life-threatening laminitis and susceptibility to infection. Although the disease cannot be cured, it is highly manageable in the majority of affected horses. By increasing the level of awareness of this common condition among horse owners, I hope that it may be recognized and treated at an earlier stage of its development, enhancing equine health and welfare and saving many horses from the ravages of acute and

chronic laminitis.

What is Equine Cushing's Disease?

Equine Cushing's disease is a neurodegenerative disorder that affects more than 40% of older horses. The disease affects the brain and pituitary gland, causing gradual progressive overproduction of pituitary hormones. The resulting hormone imbalances lead to gradual development of a wide range of symptoms: a long haircoat that eventually fails to shed according to normal seasonal patterns; persistent sweating; muscle wasting, especially along the topline; lethargy; weight loss; acute or chronic laminitis; infertility; abnormal fat distribution, with accumulations in the crest of the neck, tail head, sheath and above the eyes; consumption of large volumes of water and passage of large amounts of urine; delayed wound healing; and increased susceptibility to infections. The disease tends to occur in middle-aged and geriatric horses; most horses are approximately 15 - 20 years old at the time of diagnosis. Without treatment, symptoms gradually worsen over time and many horses are eventually euthanized as a consequence of laminitis, recurrent foot abscesses or severe bacterial infections such as pneumonia, peritonitis, or hepatitis.

What Causes Equine Cushing's Disease?

In dogs and humans, Cushing's disease is caused by a hormone-secreting tumor of the anterior part (pars distalis) of the pituitary gland at the base of the brain. In horses, by contrast, the disease involves the intermediate part (pars intermedia) of the pituitary. This portion of the gland is comprised of different hormone-secreting cells than are present in the anterior pituitary, accounting for a different hormone profile in equine Cushing's disease as compared to humans and dogs. In affected horses, the pars intermedia produces excessive amounts of pro-opiomelanocortin (POMC) and a variety of derivative hormones, including adrenocorticotrophic hormone (ACTH), lipotropins, melanocyte stimulating hormones (MSH), and endorphins. Function of the pars intermedia is normally kept in check by dopamine-secreting nerve cells within the hypothalamus, a nearby part of the brain that regulates a variety of body functions such as thirst, hunger, body temperature, water balance and blood pressure. In equine Cushing's disease, the pituitary gland is not cancerous, but simply enlarged and overactive as a result of faulty regulation by the hypothalamus. In fact, the most effective available medication for the disease, pergolide, works by mimicking the inhibitory effects of dopamine on the pituitary gland.

In dogs and humans, the major hormone produced by the abnormal pituitary gland is ACTH, which stimulates the adrenal glands to produce large amounts of the stress hormone cortisol,

which is normally released briefly and at low levels to help the body respond to short periods of physical, emotional or environmental stress. Sustained oversecretion of cortisol is responsible for most of the clinical signs of Cushing's disease in those two species. In equine Cushing's disease, by contrast, levels of cortisol are not consistently elevated, indicating that POMC derivatives other than ACTH play an important role in disease development. In view of the significant biological differences between human and canine Cushing's disease and the equine version, the name pituitary pars intermedia dysfunction (PPID) is now favored among many veterinary scientists to describe the disease in horses.

Diagnosis of Equine Cushing's Disease

In advanced cases characterized by a long non-shedding haircoat and other classical signs of Cushing's disease, diagnosis is relatively straightforward and may not require specialized testing. Diagnosis of early cases that lack obvious symptoms, however, is considerably more difficult. A variety of endocrinologic tests have been promoted for this purpose, but few have been scientifically validated in horses for which the diagnosis has been subsequently confirmed by necropsy examination. The two most practical and accurate tests currently available are: (1) the dexamethasone suppression test, and (2) measurement of ACTH levels in the blood. Unfortunately, both of these diagnostic tests have significant limitations and careful interpretation of the results by your veterinarian is critical.

The dexamethasone suppression test is an overnight protocol in which a pretreatment blood sample is collected in the late afternoon, after which a low dose of dexamethasone is administered by intramuscular injection. A second sample of blood is collected the following day at around noon and both samples are submitted for measurement of cortisol. In normal horses, administration of dexamethasone stimulates a negative-feedback response that suppresses secretion of cortisol from the adrenal glands, yielding a much lower concentration in the second blood sample. In horses suffering from Cushing's disease, however, the negative-feedback response is blunted and much less suppression, if any, is observed. Although it is generally considered the most accurate test currently available, the dexamethasone suppression test has two significant drawbacks that limit its use in some cases: (1) it requires two visits to the farm by the veterinarian, which increases its cost to the owner, and (2) many owners and veterinarians fear that administration of dexamethasone might increase the risk of laminitis in a horse that is already predisposed to its development. For these reasons, many veterinarians prefer an alternative test, measurement of plasma ACTH.

ACTH testing involves collection and analysis of a single blood sample; the pituitary gland in affected horses secretes excessive amounts of ACTH into the bloodstream as compared to normal horses. While useful, this test is generally considered to be somewhat less accurate than the dexamethasone suppression test, and blood samples must be handled very carefully to avoid degradation of ACTH and falsely low values. In addition, stress and pain due to conditions

such as laminitis may result in falsely elevated values, clouding interpretation of the results.

Neither of these tests are very sensitive in the early stages of disease development, meaning that test results can be normal in horses that are suffering ill effects of the disease, including laminitis. Furthermore, both tests are susceptible to false-positive results during the autumn months (September through December), as many unaffected horses exhibit abnormally high levels of POMC hormones at this time of year. This is believed to be the result of normal physiological hormone changes related to metabolic preparations for winter. For the horse owner and veterinarian, this “seasonal rise” in pituitary hormones means that test results will be most accurate in the winter, spring, and summer, and results of tests performed in the fall months must be interpreted carefully. Unfortunately, this seasonal rise also serves to aggravate Cushing’s disease in affected horses, and worsening of symptoms is often seen during this period. When unexplained laminitis occurs in aged horses during autumn months, Cushing’s disease should be strongly suspected.

Supplemental tests that are recommended in suspect cases of Cushing’s disease include measurements of blood glucose and insulin. Many affected horses are insulin resistant and some are significantly hyperglycemic; early recognition and tracking of these abnormalities will aid in decisions regarding nutritional management of the disease, and provide additional criteria by which to evaluate the horse’s response to treatment.

Treatment of Equine Cushing’s Disease

Optimal management of Cushing’s disease involves a combination of both specific medication to normalize the function of the pituitary gland and supportive care to address and prevent complications associated with the disease. In both cases, management will be life-long as there is no way to reverse the disease process. In the early stages, specific medication may not be required and conservative measures such as body clipping to remove the long haircoat, strict attention to diet, and scrupulous attention to teeth, hooves and preventive care may be sufficient to provide good quality of life.

In both mildly and severely affected horses, the importance of early diagnosis and aggressive treatment of bacterial infections cannot be overstated. Medications used to treat this condition focus on reducing the amount of ACTH and other POMC-derived hormones secreted by the pituitary gland. The drug of choice is pergolide, a compounded medication that mimics the inhibitory effect of dopamine on the pituitary gland, normalizing the level of hormone production. This medication is reasonably priced and well tolerated by the majority of horses. An initial dose of 0.002 mg/kg (approximately 1 mg for a 1000-lb horse) once daily is recommended for most horses; this dose may be gradually increased if significant improvement of symptoms is not

seen after 6 – 8 weeks of therapy. Since this medication serves to control the disease rather than cure it, therapy must be continued for life or symptoms will return. Many horses require periodic increases in their pergolide dose as they age.

A favorable clinical response to therapy will be associated with improvement in clinical symptoms, and improvement or normalization of dexamethasone suppression and plasma ACTH test results. Early cases or those characterized by seasonal exacerbation of clinical signs may benefit from intermittent courses of therapy, but most cases benefit from continuous treatment for the life of the horse. To ensure that a horse's pergolide regimen remains optimally effective, I recommend that dexamethasone suppression or ACTH tests be repeated annually during the summer months to monitor the effectiveness of treatment. If dose increases are required, they may then be implemented prior to the onset of the autumnal seasonal rise.

Occasional severe cases benefit from combination treatment with both pergolide and cyproheptadine (Periactin®). Trilostane, an inhibitor of adrenal cortisol synthesis, has shown promise in clinical trials conducted in the United Kingdom, but this drug is expensive and does not address the underlying problem within the brain, or the effects of POMC hormones other than ACTH.

For affected horses that are also insulin resistant, sweet feed and other feedstuffs high in soluble carbohydrates should be avoided in favor of diets that emphasize fiber and fat. Feeds containing high levels of starch, sugar, or molasses should be avoided unless needed to encourage the horse to eat.

Conclusion

Although equine Cushing's disease is incurable at present, it is highly manageable through daily administration of pergolide, an inexpensive medication that normalizes pituitary hormone secretion. This medication can transform the appearance, health, soundness, and quality of life of affected horses, and should be implemented as early in the course of disease as possible. Owners and veterinarians who monitor their middle-aged and geriatric horses closely for symptoms of this disease are best able to recognize it at an early stage, prevent serious consequences such as laminitis and severe bacterial infections, and maximize the health and wellness of their aging friends.