

Advances Against Cushing's Disease

New therapies, along with improved diagnostic tests, are clearing the way to better care.

By Janice Posnikoff, DVM

With advances in veterinary medicine, we have an increased understanding of diseases that strike our horses. Equine Cushing's disease has been recognized for more than 70 years, but has often been misunderstood. Today, however, with our improved diagnostic and treatment options, Cushing's horses are living longer and enjoying a better quality of life. Here's what we currently know about this disease:

What is Equine Cushing's Disease?

Over the years, the disease has had a few name changes, with equine Cushing's disease the most commonly accepted. But labels such as "equine 'Cushing's-like' disease," "equine Cushing's syndrome," "equine pituitary pars intermedia adenoma," and the most currently accepted name in the veterinary community, "equine pars intermedia dysfunction," have all been used to describe the condition.

Equine Cushing's disease is a primary problem of the pituitary gland, located inside the brain. This gland is like a dispatch center, where hormones and other chemical mediators called "proopiomelanocortin peptides" (POMC) are produced and then released into the body to control body functions. Horses with Cushing's disease have a breakdown of the control of the pituitary gland—it literally doesn't shut down and continues to produce POMC.

The overactive pituitary gland of a Cushing's horse can grow in size and even develop benign pre-tumor and tumor cells that press against the brain. In the advanced stages of the disease, this compression can be severe and cause neurological problems if the gland becomes big enough. Cushing's disease has often been described as a benign tumor of the brain, but there is still debate whether it's a tumor or hypertrophy, which is tissue enlargement as a result of increased work (similar to the way that muscles enlarge from exercise). Indeed, the pituitary gland can develop cells that grow to become a tumor, but it's unknown which comes first, hypertrophy or the tumor.

An overactive pituitary gland also affects the horse's adrenal glands (located near the kidneys). Stimulated by increased POMC production, the adrenal glands overproduce cortisol, which contributes to a host of health problems. Increased cortisol levels have been the traditional marker for detecting and diagnosing equine Cushing's disease.

New research is leading to a lot of answered questions and development of new questions for this disease. It's now known that specific nerve cells in the brain secrete dopamine. In normal horses these cells inhibit an overactive pituitary gland and are present in large numbers. Horses with Cushing's disease have dopamine-producing cells with decreased antioxidation capacity that are more susceptible to dying. But the question remains as to why. What is known is that fewer dopamine-producing cells means pituitary gland activity goes unchecked.

Clinical Signs

The classic Cushing's case is an old, skinny, hairy horse that grows a long, wavy hair coat year-round. Many people unwittingly believe that their horses are just getting older. In reality these horses are often sick. Along with being very hairy, Cushing's horses are generally lethargic, sweat easily, tend to run high temperatures, drink and urinate excessively, and have fertility problems. Horses with this disease are also at increased risk of developing laminitis. The high cortisol levels in the body lower the immune system, making the horse more susceptible to infections, such as delayed healing, reoccurring hoof or tooth abscesses, sinus infections and chronic fungal, bacterial or parasite infections. Pneumonia is even possible.

As Cushing's disease progresses, more and more body changes occur, and symptoms become more obvious. This can take years to happen and it's really a snowball effect. Cushing's horses metabolize protein at a higher rate that causes muscle breakdown and wasting, which can be very noticeable along the topline and haunches as the disease progresses. Weakened abdominal muscles become stretched from the weight of the intestines, creating a "pot belly" appearance. Intermittent front limb stiffness can also be seen.

In the advanced stages of the disease, severe neurological problems can occur if the pituitary gland becomes big enough and causes compression in the brain. Symptoms of compression include ataxia (uncoordinated movement of the limbs), fever, hyperventilation and possibly recumbency leading to death. If treatment is not provided—and sometimes even if it is—the pituitary gland gets larger, the immune system weaker and the body condition worsens to the point of real

debilitation for the horse. These horses look and act very old. Their hair coats are extremely long, sometimes several inches long, and very wavy. They breathe heavily and sweat in their stalls and seem extremely lethargic. They might start to sway when walking, and in the most extreme cases get to the point where they can't get up.

Disease Diagnosis

There are several ways to diagnose equine Cushing's disease. The classic method is to measure body cortisol levels in response to an outside stimulus, most notably dexamethasone (a corticosteroid). Dexamethasone, when administered to a healthy horse, tells the pituitary gland to shut down. Horses with Cushing's disease don't respond to dexamethasone stimulus—their pituitary glands continue to produce POMC, and their adrenal glands continue to produce high levels of cortisol. This dexamethasone testing procedure is known as the "dexamethasone suppression test." The higher the dose of dexamethasone used, the more the pituitary gland should be suppressed.

There are actually two types of "dex" suppression tests: high-dose dex suppression and low-dose dex suppression. It may seem obvious that the high dose is more accurate and should be the test of choice, but it's not without its complications: The biggest risk is increased chance of developing laminitis. For this reason researchers and clinicians alike are trying to find alternative ways to test for equine Cushing's disease. And they have found a few.

One alternative is the low-dose dex suppression test. This test has become the standard and is theoretically safer, due to the lower dose of dexamethasone, especially for the horse that has already had an episode of laminitis. Some researchers suggest avoiding the test during autumn months, as hormone levels in horses can vary seasonally. During fall, researchers are pointing to a higher possibility of false-positive results.

Taking it to the next level, a new test is being developed that combines thyrotropin-releasing hormone and dexamethasone, referred to by some veterinarians and researchers as the "DST/TRH" test. This test allows for increased accuracy in testing in the early stages of the disease.

Other testing methods have also been developed, mostly in an effort to avoid administering dexamethasone to horses that have laminitis or are at greater risk of developing it. One such method is to evaluate the levels of ACTH (adrenocorticotropic hormone) in the body, which has been shown to be higher in Cushing's horses. Unfortunately, this test can have false negatives, meaning even though the ACTH levels are low, the horse can still have Cushing's—the disease is just not advanced enough for the test to pick up on it.

There are researchers who suggest that high insulin levels in the horse are an indicator of this disease, and some research is being devoted to testing cortisol levels in saliva.

Another test monitors and measures the day and night levels of cortisol. In normal animals it's been shown that morning levels of cortisol are high, and in the evening levels drop off. The difference between morning and night should be more than 30 percent; if not, it's theorized that the cortisol remains at a constant level as a result of the pituitary gland not shutting down.

One final method used quite often in the field is response to treatment. Instead of testing what appears to be an obvious case of Cushing's, a veterinarian treats the horse with medication and watches for clinical signs to resolve. This has its drawbacks, especially if we are mistaking the disease for something else that should have a completely different treatment.

Treating the Cushing's Horse

A few drugs have emerged for treating equine Cushing's disease that are better than others. Today, the most commonly used drug for treating the disease is pergolide. This drug, also used to treat Parkinson's disease in humans, stimulates dopamine release, which in turn tells the pituitary gland to shut down. There are good anecdotal results and very limited side effects with this drug, as well as a lot of research available that has shown its effectiveness. In some of my patients, owners report that their horses act 10 years younger after starting treatment.

Cyproheptadine was the original drug of choice for treating equine Cushing's disease, but many studies are now showing that its effectiveness is not nearly as good as pergolide. Some reports indicate that cyproheptadine used with pergolide can be more effective, however.

A human drug called trilostane offers promise for treating equine Cushing's disease. This drug works at the level of the adrenal gland to slow down cortisol production. Current research has shown that this drug has reversed some of the symptoms of equine Cushing's disease.

More research is on the way to reproduce these findings and prove the drug's safety in horses. Trilostane is available in the

United Kingdom, and also to veterinarians here through special arrangement with drug compounding companies. At this time trilostane is very expensive, but hopefully, as has been the case with pergolide, when demand grows and efficacy and safety are established, this drug will become more available and affordable.

Diet is gaining significance in the management of Cushing's disease. Antioxidants, such as vitamins E and C, could play a role in helping to support Cushing's horses. Chasteberry (*Vitex agnus castus*) is emerging as an organic source of dopamine stimulation; while it hasn't completely stood up to the rigors of scientific testing, many researchers are still looking into it as a source of treatment for equine Cushing's disease.

Feeding a Cushing's horse can be very challenging, and unfortunately there are no set rules. However, it is safe to say that horses with Cushing's disease do well on the same type of low-sugar, low-starch diet that horses prone to laminitis do. This type of feeding plan usually rules out alfalfa and grain, and leaves us with grass hay and grass hay pellets. If the disease symptoms aren't too severe, then extruded feeds utilizing soy and beet pulp can help keep weight on. Generally I try to keep Cushing's horses on mostly timothy and orchard hays, along with pelleted feeds, like those mentioned above, to keep weight on, and I minimize sugar as much as possible. Since Cushing's horses are difficult to keep weight on, dedication has to be put into balancing diet with exercise.

Insulin Resistance

One real misconception about Cushing's disease is that affected horses are hypothyroid and fat. They're not. We don't know enough about the thyroid gland and its hormones, but currently it's believed that the thyroid does not play a direct role in equine Cushing's disease. In the past, many older horses that were "easy keepers" were diagnosed with Cushing's disease and put on thyroid medication. Thyroid supplementation hasn't been proven to help horses with Cushing's disease. In fact, many horses that are true hypothyroid are not fat at all and can often be thin.

It is the horse with insulin resistance that is fat. Insulin resistance is fast becoming a buzzword as the culprit behind easy keepers. The pituitary gland has nothing to do with this disease. Instead, as its name suggests, cells become resistant to insulin. When this happens, sugar (carbohydrates) circulating in the bloodstream is no longer drawn into the cells by insulin. This leaves excess sugar in the blood that gets converted to fat. In horses this often causes a cresty neck and large fat pads in abnormal places. Mustangs are genetically engineered for this condition so that they can put on fat stores in times of plenty to rely on when food is sparse. This leads us to believe that genetics play a large role in insulin resistance.

The trouble with modern horsekeeping is that we often provide plenty of food all the time for our beloved equines, so they just keep making fat stores—some better than others. Insulin resistance can create dire health problems, especially in the hoof, where laminitis can occur.

In the End

Cushing's is an easily recognized and treatable disease, but unfortunately it can't be cured yet. It is a slow-progressing disease that often goes unrecognized in the early stages. Sadly, Cushing's disease usually gets diagnosed once the clinical signs are more advanced. When caught early, treatment is very successful in reducing clinical signs and allowing affected horses to live almost normal lives. For those horses in advanced stages of the disease, treatment still offers improved quality of life and longevity.

This disease hits close to home for me since my own horse Prophecy was diagnosed with it at the age of 9 using the morning and night cortisol levels testing method. I have had him on pergolide since that time, which was about four years ago. His symptoms at the time of diagnosis were for the most part very mild and very subtle. He had many episodes of "ain't doing right," laziness in the arena and a mild case of laminitis. His owner at that time, having had a dog with Cushing's disease, asked me to test him. I'm happy to report that he is symptom free today. However, to be on the safe side, I'm starting Prophecy on higher dose vitamin E supplements and will test him using low-dose dexamethasone suppression combined with TRH stimulation. If he tests positive with that method, I will seriously consider trilostane for him.

In my practice area, horses with Cushing's disease do very well and can lead an active lifestyle. Those undergoing treatment do much better for a longer period with fewer problems; I rarely have to deal with laminitis in these horses. I have one 18-year-old Grand Prix dressage horse with Cushing's disease that is still competing and doing well. She has been on pergolide for three years, but we are starting to see a few more symptoms, so we are increasing her dosage and are considering trilostane for her.

Overall, horse owners shouldn't fear this disease, but we must all have a healthy respect for it.

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