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## Testing for Equine Cushing's Disease

### Weighing the pros and cons of pituitary pars intermedia dysfunction tests old and new

In decades past, owners and veterinarians simply attributed many conditions for which nothing could be done to "old age." Today we have specific diagnoses and treatments for several of these once-hopeless issues. One such disease is pituitary pars intermedia dysfunction (PPID), also referred to as equine Cushing's disease. Australian researchers recently estimated that PPID occurs in 21% of horses over age 15, and animals in this age group are at an increased risk of developing the condition.

Veterinarians can diagnose advanced PPID based on a horse's physical appearance. Andy Durham, BSc, BVSc, CertEP, DEIM, Dipl. ECEIM, MRCVS, a partner at Liphook Equine Hospital, in the U.K., and a leading equine Cushing's specialist, reports, "The commonest signs are laminitis, muscle wastage, slow or incomplete shedding of a long, curly winter coat, susceptibility to infections, and excess thirst with excess urination."

Nicholas Frank, DVM, PhD, Dipl. ACVIM, professor of large animal medicine at Tufts Cummings School of Veterinary Medicine, adds that PPID is a particular concern in horses that already suffer from insulin problems (insulin is an important hormone responsible for regulating the blood concentration of glucose, the body's most important fuel molecule) as part of equine metabolic syndrome (EMS, a metabolic and hormonal disorder characterized by obesity, regional adiposity, insulin resistance, and laminitis).

Horses with advanced PPID might also display personality changes, lethargy, and increased appetite. Due to abnormal fat redistribution consistent with the disease, these horses might appear pot-bellied, with muscle loss over the topline and bulging fat pads above their eyes. But clinical signs of early disease progression are far more variable and subtle.

"Characteristic pituitary changes of PPID develop prior to the onset of these recognizable clinical signs," Durham says. "Many cases are subclinical (inapparent) in the early stages."

Frank, who runs a service at Tufts dedicated to diagnosing and treating equine endocrine problems, says, "Diagnostic testing for PPID has advanced, and we are now in much better position to diagnose this disorder at an earlier time point." He and others are examining tests to identify PPID horses in the earliest disease stages to facilitate timely intervention, resulting in a more comfortable horse. In this article we'll break these tests down for you.

### Adrenocorticotropic Hormone Testing

At present, the most common approach to diagnosing PPID is a blood plasma test for adrenocorticotropic hormone (ACTH). "ACTH is a hormone normally made in relatively small amounts by the pituitary gland to control the function of the adrenal glands (located adjacent to the kidneys and involved in the secretion of several important hormones)," Durham explains. "When the pituitary gland is affected by Cushing's disease, overproduction of ACTH is detectable as higher ACTH concentrations in a blood sample."

Until recently, many believed ACTH testing in the autumn months could lead to interpretation errors because from August to October even normal horses produce ACTH concentrations that are a bit higher than the rest of the year.

However, "looking at samples collected in the autumn may actually be the most revealing due to more profound seasonal increases of PPID horses compared to normal horses," says Dianne McFarlane, DVM, PhD, Dipl. ACVIM, associate professor of physiological sciences at Oklahoma State University's School of Veterinary Medicine.

She suggests that labs have a seasonal reference interval that accounts for this normal "biostimulation." Recent study results indicate that normal horses living at more southern latitudes might experience even higher ACTH levels during autumn months than those in northern latitudes.

Durham lists other important guidelines when using ACTH as a testing parameter: "ACTH concentrations may also increase in horses affected by severe stress (e.g., during transport), severe illnesses or pain, or recent strenuous exercise. Less severe stress and pain such as occurs with most laminitis cases doesn't have a marked effect on ACTH. Sedation prior to testing might affect results but feeding does not."

Veterinarians can collect blood samples for ACTH any time of day and do not need to fast the horse first as they do with some other protocols such as insulin testing. Sample handling specifics, however, are important. Both Durham and McFarlane advise that plasma (centrifuged from the collected blood) should be chilled within three hours and shipped to the lab on ice. If centrifugation isn't available, it's possible to employ gravity separation of plasma, chill the sample, and then notify the lab of the need to centrifuge the sample upon receipt. "Otherwise," says Durham, "incorrectly handled gravity-separated samples will produce falsely high ACTH results."

### Insulin Testing

Insulin resistance (IR, a reduction in a horse's sensitivity to insulin that makes it harder for the fat, muscle, and liver cells to transport the glucose out of the bloodstream and store it as glycogen) occurs in about one-third of horses with PPID, says McFarlane. In light of IR's prevalence and its significance in identifying laminitis risk, veterinarians frequently measure fasting insulin levels (a test that involves one measurement after withholding feed overnight) along with ACTH. However, Durham cautions, "This is not a very useful test since about 75% of PPID cases have normal fasting insulin despite demonstrating insulin resistance in other dynamic tests (requiring multiple steps/measurements), such as the oral sugar test or the combined insulin-glucose test (CGIT)."

While the fasting insulin test has been practical in the past due to its ease and accessibility, Durham says, "The oral sugar test is ideal to demonstrate IR in PPID cases."

He suggests that insulin testing also has value as a prognostic indicator for laminitis risk in PPID-affected horses. And insulin testing helps practitioners advise owners about planning these horses' diets.

### Overnight Dexamethasone Suppression Test

Historically, veterinarians have considered the overnight dexamethasone suppression test (ODST) the "gold standard" for PPID diagnosis. But Durham says researchers haven't shown evidence to support this. "The ODST and ACTH are probably very similar in sensitivity and specificity (likelihood of presenting false negatives and positives) outside the autumn months, but ODST cannot be used in the autumn due to a lack of seasonal adjustment of interpretation," he says. "Perhaps another important reason why practitioners have moved away from this test is that it requires two visits to see the horse whereas ACTH is tested during one visit."

"The ODST requires two visits to see the horse, whereas ACTH is tested during one visit."

Dr. Andy Durham

McFarlane says the ODST does have some merits: "While it is not superior to measuring ACTH concentration, it will diagnose some PPID horses in which plasma ACTH concentration is normal. While it performs very well in identifying late-stage PPID, recent studies show that the ODST is not useful in earlier cases of PPID."

There has also been pushback from practitioners about using the ODST due to concerns that it might induce laminitis in PPID horses with insulin resistance. "It is unlikely that administration of a single dose of dexamethasone at the dose used in the test will cause laminitis, but high doses of steroids have long been suspected of contributing to laminitis in highly susceptible populations," says McFarlane.

Durham says horses with other laminitis risk factors, such as EMS, probably are at a higher risk of developing laminitis post-ODST than healthy animals, but veterinarians will likely test these at-risk cases anyway.

### Blood Chemistry Panels and Complete Blood Counts

As a veterinarian works to diagnose PPID, he or she might order blood chemistries and complete blood counts. McFarlane encourages such blood screening tests: "Changes on routine chemistry panels due to PPID are uncommon. However, horses with PPID are at risk of secondary conditions, especially infections or abscesses. Therefore, a health check that includes routine blood work is recommended to assess overall health."

While the results might help rule out infections or internal organ problems, Durham agrees that they aren't reliable for diagnosing PPID: "PPID cases may sometimes demonstrate persistently elevated glucose levels as a result of failure of the pancreas to sustain insulin levels in the face of insulin resistance, but this applies to less than 10% of cases."

### Domperidone Testing

Researchers are examining domperidone administration as another possible PPID test. "Domperidone, as a dopamine blocker, stimulates pituitary secretion of ACTH," Durham says. "Horses with PPID may have a greater stimulatory response and higher magnitude of ACTH increase following dosing with domperidone."

McFarlane adds, "This test has shown some promise but needs further investigation and validation to become more widely approved. Although the number of horses evaluated is small, the evidence suggests that the domperidone test isn't a better test than any others currently in use."

### $\alpha$ -Melanocyte Stimulating Hormone ( $\alpha$ -MSH)

Another hormone researchers are considering measuring in a future test is  $\alpha$ -MSH, which is a breakdown product of ACTH that comes from the intermediate lobe of the pituitary gland—the area affected by PPID. "In contrast, ACTH is produced from two different lobes of the pituitary," says McFarlane. "Therefore in theory,  $\alpha$ -MSH is a more specific test for dysfunction of the intermediate lobe."

Durham notes, "Several studies have investigated the use of  $\alpha$ -MSH as a diagnostic test and it seems to be good."

McFarlane adds that in studies comparing ACTH and  $\alpha$ -MSH measurements to diagnose PPID, researchers found no advantage to measuring  $\alpha$ -MSH. This test is not yet commercially available.

### Thyrotropin-Releasing Hormone Stimulation Testing

"Measurement of ACTH before and after administering synthetically prepared thyrotropin-releasing hormone (TRH, which stimulates the pituitary to release ACTH), can yield diagnostic information," says McFarlane. "In a PPID horse, there will be a more profound concentration of ACTH than normal following stimulation with TRH. This is a newer test that is showing potential as an earlier indicator of PPID than the ODST or resting ACTH concentration. In horses with clinical signs of PPID that have normal resting plasma ACTH concentration, we recommend the TRH stimulation test as a dynamic, second-tier diagnostic test."

"The TRH stimulation test is a newer test that is showing potential as an early indicator of PPID than the ODST or resting ACTH concentration."

Dr. Diane McFarlane

Both Frank and Durham prefer the TRH stimulation test above all others for identifying early PPID. "Although only a few studies have examined this test thus far, it appears to have great promise and may well become the 'gold standard,'" Durham says. "One caution is that this test needs to undergo more widespread use and further evaluation. Another problem with TRH-stimulation testing is that it is also affected by season and, as yet, there are no seasonal reference intervals, making it difficult to interpret in the autumn months."

Currently, in the United States, TRH is both difficult to come by and expensive. Frank notes, however, that the problem of availability in the United States will soon be addressed. "A medical-grade TRH called protirelin was available in the past for use in humans, and two pharmacies in the U.S. have acquired the drug and will soon supply it to veterinarians." Frank is currently conducting clinical studies with protirelin to further evaluate this test.

### Take-Home Message

Obtaining an accurate ACTH diagnosis is key to managing the disease. While no test is 100% accurate, it's important that a veterinarian try to pin down a diagnosis before medicating a horse. A variety of tests are available for diagnosing PPID, though most veterinarians currently rely on ACTH testing. Scientists are working on validating a few other assays, which eventually might prove more sensitive and specific for detecting Cushing's disease.