Pituitary pars intermedia dysfunction (PPID), also known as equine Cushing’s disease, is the most common endocrinopathy of older horses, affecting 20-30% of horses over the age of 20. It develops as a consequence of degeneration of hypothalamic dopaminergic neurons that regulate (by tonic inhibition) the pituitary gland, specifically the pars intermedia (PI) that is entirely composed of a single cell type – the melanotrope. Similar to Parkinson’s Disease, progressive loss of dopaminergic innervation over many years leads to unregulated enlargement of the PI, initially by melanotrope hyperplasia and progressing to micro- and macroadenoma formation within the PI. Dopamine concentrations in the PI of horses with PPID have been shown to be one-tenth those of normal horses and tyrosine hydroxylase activity, the rate limiting enzyme for production of dopamine, is also markedly reduced in equids with PPID. Another consequence of loss of PI dopaminergic innervation is excess production of the prohormone pro-opiomelanocortin (POMC, 241 amino acids). Processing of POMC by prohormone convertase 1 and prohormone convertase 2 leads to increased amounts of many POMC-derived peptides, including ACTH1-39 (POMC138-176) and α-MSH (ACTH1-13) in jugular venous plasma. Excess amounts of POMC peptides are thought to be responsible for development of clinical signs of PPID, including a long hair coat that fails to shed, loss of muscle mass, increased drinking and urination, recurrent infections, and chronic laminitis.

**Diagnosis**

Practically, the diagnosis of PPID is most commonly made by observation of hypertrichosis and other clinical signs in older equids. However, establishing a diagnosis of PPID in less severely affected animals can be challenging. As a result, a number of endocrinologic tests have been used to evaluate horses with suspected PPID. Recently, the PPID Diagnosis Working Group of the Equine Endocrine Society developed a consensus statement (http://sites.tufts.edu/equineendogroup/files/2013/11/EEG-recommendations-downloadable-final.pdf) for the approach to diagnosis of PPID. Testing involves Tier 1 tests (screening tests) and Tier 2 tests for further evaluation of horses with inconclusive Tier 1 test results. Tier 1 tests include measurement of plasma ACTH concentration and the overnight dexamethasone suppression test and the currently recommended Tier 2 test is assessment of the ACTH response to thyrotropin releasing hormone (TRH). It warrants emphasis that the vast majority of experimental work evaluating diagnostic tests for PPID has been performed on horses; thus, extrapolation of findings to ponies and other equids has not been well validated.
Plasma ACTH concentration (Tier 1). Equids with PPID have excessive amounts of ACTH and ACTH-like peptides in abnormal PI tissue and increased amounts are released into plasma. Thus, measurement of plasma ACTH concentration is a logical choice for a single sample screening test for initial evaluation of equids suspected to have PPID. Earlier reports indicated that appropriate sample handling was critical for accurate determination of ACTH concentration; however, it is now recognized that the peptide is more stable. Collection of a blood sample into a plastic EDTA tube and placing it in a cooler or refrigerator with centrifugation and separation of plasma with 6-8 hours appears adequate. The plasma should then be frozen and sent on ice packs to the testing laboratory. Of interest, it has been shown that the “ACTH” measured in plasma from PPID-affected horses is less bioactive than ACTH in normal horses. This finding suggests that the assays used by testing laboratories may be measuring both endogenous ACTH and ACTH-like peptides that can also bind to the antibodies used in the assays. Thus, it should not be surprising that different ACTH assays (used in different labs) can yield different results. Which assay may be most “accurate” remains to be determined but a “take-home message” is that you should be consistent with the laboratory you use and interpret results using that lab’s reference intervals. A limitation of using plasma ACTH concentration is seasonal variation in test results. In normal ponies and horses without signs of PPID, plasma ACTH concentrations measured in the fall are often above the threshold for diagnosis of PPID. This “seasonal problem” initially led to a recommendation that testing in the late summer and fall months (late July through November in the northern hemisphere) should be avoided due to the for potential false-positive test results. Recently, however, it has been shown that PPID-affected horses have a more dramatic seasonal increase in ACTH in the fall (Figure 1) and that testing at this time of year, interpreting results with seasonally adjusted reference ranges, may actually be a more sensitive test to detect PPID in the earlier stages of the disease, when plasma ACTH concentration may remain normal in non-fall months.

Figure 1. Plasma ACTH concentrations measured monthly in groups of normal horses (filled squares) and PPID-affected equids (open circles) demonstrating greater seasonal increases in ACTH in fall months in PPID-affected horses; the hatched line is the seasonally-adjusted upper limit of the reference interval (from Copas VEN, Durham AE. Circannual variation in plasma adrenocorticotropic hormone concentrations in the UK in normal horses and ponies, and those with pituitary pars intermedia dysfunction. *Equine Vet J* 2012;44:440).

Dexamethasone suppression test (Tier 1): The overnight dexamethasone suppression test (ODST) is still considered by some equine clinicians to be the “gold standard” endocrinologic test to support of a diagnosis of PPID. However, this statement is not without controversy and there is concern, although poorly documented, that administration of dexamethasone may induce or exacerbate laminitis in PPID-affected equids. In its most simple form, the ODST consists of measuring cortisol in the late afternoon (typically 5 pm) followed by administration of dexamethasone (40 µg/kg, IM = 20 mg to a 500 kg horse) and subsequently measuring plasma cortisol concentration between 17 and 19 h hours later (between 10 am and noon the following day) (Figure 2). The major limitation of the ODST for ambulatory practitioners is that it requires two visits to the horse. However, considering the fact that the most important value is the cortisol concentration following dexamethasone administration, the ODST can be simplified by
dispensing dexamethasone to the client for administration and limiting the test to one visit the following morning. When using this test, it is probably wise to consider dexamethasone as a “sledgehammer” in terms of feedback to the hypothalamic-pituitary axis. In other words, failure of dexamethasone to induce suppression of circulating endogenous cortisol concentration is strongly supportive of PPID. Unfortunately, as with plasma ACTH concentration, the ODST may be less effective in diagnosis of PPID in the earlier stages of the disease when test results remain normal.

Seasonal variation can also affect ODST results but to a lesser extent than ACTH concentration. To examine the effect of season on ODST results, the author performed the test monthly for a year in a group of 18 aged horses (>19 years) without clinical signs of PPID. Seven of 18 horses had normal overnight DST results throughout the year while 11 horses had overnight DST results supportive of PPID from 1 to 9 months of the year. Test results from late July through late October were most commonly affected by seasonal variation. Thus, results of tests performed from July through November, if abnormal, should be interpreted with caution. However, it warrants emphasis that normal ODST results during late summer to fall are valid and can be useful in case assessment. A further observation in the author’s study that warrants mention is that no signs of laminitis were induced in this group of older horses during performance of 216 ODSTs.

Response of ACTH to TRH (Tier 2). TRH is a releasing hormone for several pituitary hormones. Nearly 30 years ago, administration of TRH was shown to increase plasma cortisol concentration when administered to horses and ponies with PPID. More recently, administration of TRH has also been demonstrated to result in greater increases in plasma ACTH concentration in PPID-affected equids than in normal aged equids. Because melanotropes in the PI have TRH receptors while corticotrophs in the pars distalis do not, the increase in ACTH following TRH administration can be attributed solely to release of ACTH and ACTH-like peptides from the pars intermedia. This difference has led to renewed interest in using the TRH stimulation test to support a diagnosis of PPID, especially when basal plasma ACTH concentration or results of an ODST are equivocal. The test is performed by measuring plasma ACTH concentration before and 10 minutes after administration of 1 mg of TRH IV and a positive result is an increase in ACTH above 110 pg/mL. Although the TRH stimulation test is currently being advocated as a “more sensitive” test for detection of PPID in the earlier stages of the disease, the true value of this test remains uncertain and needs to be assessed in a larger group of equids. A further reason that this test may be pursued, rather than an ODST, would be to alleviate owner concerns about possible exacerbation of laminitis following dexamethasone administration. As with the Tier 1 tests, the increase in plasma ACTH concentration after TRH administration is also greater in fall months and the ACTH threshold value, above which supports a diagnosis of PPID, has yet to be established.

Serum insulin concentration. Measurement of basal insulin concentration may be of benefit in initial evaluation of equids with suspected PPID, not because insulin concentration is either sensitive or specific for diagnosis of PPID, but because it may offer prognostic information. Specifically, one case series found poorer long-term survival in PPID-affected equids with hyperinsulinemia as compared to PPID equids with a normal insulin concentration. This makes sense because insulin dysregulation has been associated with laminitis and it is also logical that
prognosis may be poorer with multiple endocrine abnormalities than with dysfunction of the hypothalamic-pituitary-adrenal axis alone.

**Treatment**

Management of PPID-affected equids consists of improved husbandry, including adequate nutrition and limiting competition for feed, body-clipping, preventive health care, dentistry, and appropriate treatment of concurrent medical problems. In addition, specific treatment with the dopamine agonist pergolide can improve quality of life and reverse many clinical signs of PPID. Combination treatment with both pergolide and cyproheptadine, in the author’s experience, may also prove beneficial in more advanced cases. For patients with chronic laminitis, appropriate trimming or shoeing and judicious use of analgesic medications is also necessary. Further, due to the expense of lifelong medication, a decision of whether or not to treat affected horses with pergolide should be made on a case-by-case basis in consideration of the client’s goals.

At present, it is the author’s recommendation that the initial medical treatment for equids with PPID should be pergolide at a dose of 2 μg/kg, PO, q 24 hours (1 mg/day for a 500 kg horse). Of interest, clinical improvement is usually noted as a brighter attitude and an increase in energy level, often within the initial week of treatment. In some instances, “teddy bear” horses with long standing PPID that could be surrounded by small children without concern may “wake up” and owners should be warned of this possibility. If no improvement is noted within 30 days (depending on season as hair coat changes will vary with the time of year that treatment is initiated), the daily dose can be increased by 1-2 μg/kg (to 1.5-2 mg/day) with reassessment after 30 days. The author typically increases pergolide to a total dose of 6 μg/kg (3 mg/day for a 500 kg horse). If only a limited response is observed at this dose of pergolide and endocrinologic test results remain abnormal, addition of cyproheptadine (0.5 mg/kg, PO, q 24 hours) to pergolide therapy has been effective in a limited number of cases treated by the author. It is important to recognize that the rate of clinical improvement is higher than that for normalization of endocrinologic test results. For example, in a treatment study performed by the author, 13 of 20 pergolide treated horses were reported to have improved clinically while only 7 of 20 had normalization of endocrinologic test results. Thus, it is prudent to regularly measure blood glucose concentration and perform follow-up endocrinologic testing when managing equids with PPID. The author currently recommends measuring plasma ACTH concentration or performing an ODST at least yearly (between December and June in horses in the northern hemisphere) in horses that appear to be stable and 30 days after a change in medication dose or addition of cyproheptadine. Further, although pregnant mares have been treated with the drugs, safety of drug use during pregnancy has not been studied in equids.

As with many chronic diseases in the horse, specific nutrient supplementation and complementary or alternative therapies, including acupuncture, homeopathy, and herbal remedies, have been recommended and used in equids with PPID. A herbal product made from chasteberry has also been advocated for treatment of PPID. However, the claim was supported with a series of case testimonials in which the diagnosis of PPID was poorly documented and a field study demonstrated that this herbal product was ineffective for treatment of PPID.