IS THERE MORE TO PPID THAN OLD SHAGGY HORSES?

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Introduction

Pituitary pars intermedia dysfunction (PPID), or equine Cushing's disease, is being recognized with increasing frequency. It develops because of loss of hypothalamic dopaminergic neurons, with parallels to Parkinson's Disease. Diagnosis of PPID in advanced cases is straightforward, but diagnosis in earlier stages of the disease remains challenging.

Learning Objectives

1. State expected prevalence of PPID in horses over 20 and 30 years of age
2. Explain the pathophysiology and progression of PPID
3. Recognize the range of clinical signs attributable to PPID
4. Understand the endocrine tests available to support a diagnosis of PPID
5. Describe the limitations of current endocrine tests

Prevalence of PPID

Although recognition and treatment of pituitary pars intermedia dysfunction (PPID) in horses has clearly increased over the past couple of decades, there is no evidence that the prevalence of PPID is truly increasing. Increased recognition of the disease is likely a consequence of clients maintaining their horses to more advanced ages as well as improved health care (e.g., diet and dentistry) being provided to older horses. Recent surveys of horse owners in Queensland, Australia and the United Kingdom revealed prevalence rates of 15-20% of PPID in horses and ponies 15-20 years of age, increasing to nearly 30% in horses over 30 years of age. There is no gender predilection and average age of affected horses is around 20 years. All breeds and types of equids can be affected with PPID, but ponies appear to be at greater risk.

Pathophysiology

In humans and dogs, Cushing's disease most commonly develops due to a corticotrope adenoma in the pars distalis of the pituitary gland (PG). These adenomas are thought to arise spontaneously. In contrast, Cushing's disease in horses is almost exclusively attributed to melanotrope hyperplasia or adenoma formation in the pars intermedia (PI) due to progressive loss of hypothalamic innervation over many years. Abnormal PI tissue in horses contains markedly reduced amounts of dopamine, about 10% that of normal PI tissue, consistent with a specific loss of hypothalamic dopaminergic innervation. Further, tyrosine hydroxylase activity, the rate-limiting enzyme for production of dopamine, is also markedly reduced in equids with PPID. Recent evidence suggests that this loss of dopaminergic innervation is due to oxidant-induced injury to hypothalamic tissue. Further, insoluble aggregates of the neural protein α-synuclein have been found in dopaminergic nerve terminals of PPID-affected horses. These protein aggregates are also found in humans with Parkinson's disease,

suggesting that the two neurodegenerative disorders may share a similar pathogenesis. However, the population of neurons affected in horses, as compared to humans, appears to be different leading to the difference in clinical signs observed in each species.

In normal equids, hypothalamic dopaminergic neurons exert tonic inhibitory action on PI melanotropes. Progressive loss of dopaminergic innervation over years leads to enlargement of the PI in equids with PPID, initially by melanotrope hyperplasia and progressing to micro- and macroadenoma formation within the PI. A 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 $ACTH_{1-39}$ ($POMC_{138-176}$) and α-MSH ($ACTH_{1-13}$) in jugular venous plasma. Excess amounts of POMC peptides are thought to be responsible for development of the variable clinical signs of PPID, although actual pathophysiology remains poorly understood.

Clinical Signs

The pathognomonic clinical sign of PPID in horses is hypertrichosis, a long and curly hair coat that fails to shed. In some affected horses, coat color changes have also been observed. The pathogenesis of hypertrichosis, characterized by arrest of hair follicles in anagen, remains unclear. Abnormal sweating, both hyperhidrosis and anhidrosis, is also observed in up to two-thirds of horses with PIPD. Weight loss and lethargy, or poor performance, can also be observed in horses with PPID. In addition to true weight loss, protein catabolism due to increased cortisol activity leads to loss of muscle mass. This is most notable in advanced cases as a loss of epaxial and rump musculature. Despite weight loss, appetite in affected horses is normal or even increased (polyphagia). However, dental abnormalities, leading to painful mastication and quidding, may compromise feed intake and contribute to weight loss in some horses. Combined with, or often preceding, loss of muscle mass in some horses is deposition of fat along the crest of the neck, over the tail head, and in the sheath of male horses. Another area where abnormal fat deposition may occur is above and behind the eyes (supraorbital area). Horses with PPID have also been described as overly docile and more tolerant of pain than normal horses. The latter signs have been attributed to increased plasma and cerebrospinal fluid concentrations of β-endorphin that are 60- and more than 100-fold greater, respectively, in horses with PPID than in normal horses. An occasional equid with PPID may also have marked hyperglycemia, hypertriglyceridemia, and elevated hepatic enzyme activities detected on a serum biochemical profile. These laboratory abnormalities may go unrecognized if blood work is not pursued as there are no specific clinical signs that would alert a clinician to these concurrent problems.

Chronic, insidious-onset laminitis is perhaps the major clinical complication of PPID with more than 50% of horses affected in most reports. Although the condition is more amenable to management in ponies due to their lower body weight, chronic or recurrent pain with laminitis and associated foot abscesses is often the reason for euthanasia in equids with PPID. Polydipsia and polyuria (PU/PD) develop in about one-third of horses

with PPID. Equids with PPID tend to have delayed wound healing and are frequently affected with secondary infections. Commonly recognized infections include skin infections (e.g., refractory “scratches” and fistulous tracts), recurrent subsolar abscesses, conjunctivitis, sinusitis, gingivitis, alveolar periostitis, and bronchopneumonia.

Other signs that have been reported in horses with PPID include persistent mammary secretions and infertility. Central nervous system (CNS) dysfunction, including ataxia, blindness, and seizure-like activity, are occasionally observed in equids with PPID. A major complication of hypercortisolism in affected human patients is osteoporosis. It is interesting to note that euthanasia of horses with PPID has been reported due to development of pelvic, pedal bone, mandibular, and multiple rib fractures. Finally, recent reports have implicated PPID as a contributing factor to flexor tendon and suspensory ligament degeneration in older horses.

Overall, PPID is a heterogenous disease with varying clinical manifestations. Although the classic case of a “wooly mammoth” is clearly recognizable, clinicians should consider PPID as a contributing factor to wider variety of clinical complaints advanced by owners of aging equids.

Diagnosis of PPID

Practically, the diagnosis of PPID is often made by observation of hypertrichosis and other clinical signs in older equids. In fact, hair coat changes remain the most accurate characteristic to establish a diagnosis of PPID. When clinical signs are supportive of PPID, confirmatory endocrine testing is not always necessary. However, pursuit of endocrine testing (baseline ACTH concentration, see below) can provide initial data that can be useful for assessing response to treatment over time. Further, it is useful to determine whether blood glucose and serum insulin concentrations may be abnormal, as this information would have prognostic value. Additional diagnostic evaluation that warrants consideration includes a thorough oral exam as well as hoof radiographs because equids with PPID may have radiographic evidence of chronic laminitis despite absence of lameness. Last, fecal egg counts to assess parasite burden are warranted because equids with PPID may be more susceptible to parasitism.

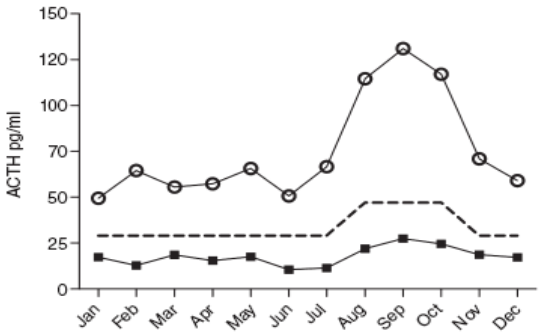
At post-mortem, PPID is diagnosed by documenting enlargement of the PG. The PG of most horses weighs 1.5-2.5 g, but the PG can more than double in size and weight with expansion of the diseased pars intermedia. A grading system of 1 (normal) to 5 (PI with a macroadenoma > 1 cm in diameter) has been established to document the severity of PPID. Expansion of the PI leading to enlargement of the PG likely progresses over a decade or longer and many middle-aged horses have histological evidence of PPID (grades 2-4) with no clinical signs. Thus, there is somewhat of a disconnect between post-mortem findings and clinical evidence (clinical signs) to support a diagnosis of PPID. As a consequence, a true “gold standard” diagnostic criterion for PPID remains controversial.

In contrast to the “wooly mammoth” PPID equid, establishing a diagnosis of PPID in equids with subtle clinical signs can be challenging. As a result, several endocrinologic tests have been used over the years to evaluate horses with suspected PPID. In 2021, the Equine Endocrinology Group updated a consensus statement for the approach to diagnosis of PPID (*http://sites.tufts.edu/equineendogroup)*. Currently recommended testing involves a Tier 1 screening test (measurement of plasma ACTH concentration) and a Tier 2 dynamic test for further evaluation of horses with inconclusive Tier 1 test results. The currently recommended Tier 2 test is assessment of the ACTH response to thyrotropin releasing hormone (TRH). It warrants emphasis that most of the 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 screening test): 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. Plasma ACTH concentration in PPID-affected equids appears to have minimal diurnal variation allowing sample collection any time of day. Blood samples are collected into plastic EDTA tubes and placed in a cooler or refrigerator until centrifugation and separation of plasma within 6-8 hours. The plasma should then be 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 laboratory’s reference intervals. An important limitation of using plasma ACTH concentration to support a diagnosis of PPID is that values often remain below the upper limit of the “normal” reference range in earlier stages of disease. Specifically, many equids with grade 2-4 histological evidence of PI enlargement may have normal plasma ACTH concentrations, or a false-negative result.

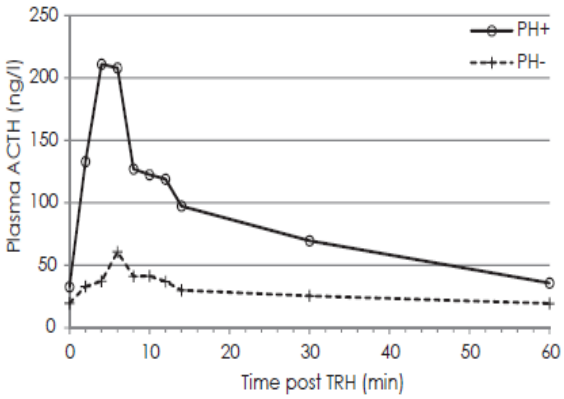
Another limitation of using plasma ACTH concentration is seasonal variation in test results. In normal ponies and horses without signs of PPID, plasma ACTH concentrations measured in the fall are often above the threshold for diagnosis of PPID. This “seasonal problem” initially led to a recommendation that testing in the late summer and fall months (July through November in the northern hemisphere) should be avoided due to the potential for false-positive test results. However, it is now recognized that PPID-affected horses have a more dramatic seasonal increase in ACTH in the fall and that testing at this time of year and interpreting results with seasonally adjusted reference ranges, may 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**).

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. *Equine Vet J* 2012;44:440).



Response of ACTH to TRH (Tier 2 dynamic test): 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 (**Figure 2**). Because melanotropes in the PI have TRH receptors while corticotropes 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 PI. 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 results are equivocal. The test is performed by measuring plasma ACTH concentration before and 10 minutes after administration of 1 mg of TRH IV (500 kg horse). 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 needs to be assessed in a larger group of equids. 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 in fall months, has yet to be established.

Figure 2. Median plasma ACTH responses to 1 mg TRH IV in 44 horses with PI hyperplasia (PH+, open circles and solid line) and 22 horses with normal pituitary glands (PH-, + and dashed line) (from Durham AE et al. *Equine Vet Educ* 2014;26:216).



Serum insulin concentration: Measurement of basal insulin concentration is also recommended during 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. Another recent study found an association between

serum insulin concentration and severity of laminitis. Thus, the prognosis for long-term successful management of equids with PPID is more guarded when PPID is accompanied by insulin dysregulation and laminitis. Curiously, why some equids with PPID have evidence of insulin dysregulation and develop laminitis while others do not remains poorly understood.

References/Suggested Reading

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